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**CHARACTERISTICS OF ORAL FUNGAL INFECTIONS
AND QUALITY OF LIFE IN PATIENTS WITH HEAD AND
NECK CANCER UNDERGOING CONCURRENT
CHEMORADIOTHERAPY**

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THESIS INTRODUCTION

1. Introduction

Head and neck cancer (HNC) is the seventh most common malignancy worldwide and is associated with a high mortality rate in developing countries. According to the World Health Organization, approximately 439,000 new cases of oral and oropharyngeal cancer are projected to be diagnosed by 2030. Concurrent chemoradiotherapy (CCRT) is the standard treatment for non-metastatic HNC; however, it frequently induces oral and oropharyngeal mucositis, leading to dysphagia and increasing the risk of oral fungal infections, thereby exacerbating disease-related morbidity. These adverse effects negatively impact patients' nutritional status and quality of life (QoL). Meanwhile, QoL is a crucial indicator that comprehensively reflects overall health status and disease progression and serves as an important guide for clinical decision-making. In Vietnam, although several studies have addressed QoL in cancer patients, data on QoL in patients with HNC remain limited, and no studies have specifically evaluated the impact of oral fungal infections on QoL in this patient population..

Oral fungal lesions (oral candidiasis, OC) are a relatively common health condition, most frequently caused by *Candida* species. In healthy individuals, the oral colonization rate of *Candida* spp. may reach up to 75%, where these organisms exist as commensals and typically do not cause any tissue damage. However, when local and systemic immune defenses are compromised, *Candida* spp. can proliferate and induce oral mucosal lesions, leading to local discomfort, pseudomembranous plaques, burning pain, altered taste sensation, and difficulties in eating and swallowing. These manifestations may result in prolonged hospitalization or, in severe cases, progress to invasive fungal infections and systemic candidiasis, which are associated with high mortality rates. Therefore, early detection and prevention of oral fungal infections are crucial to prevent adverse clinical outcomes, thereby improving patients' QoL and prolonging survival..

In Vietnam, the prevalence of OC among cancer patients in general ranges from 43.07% to 45.8%. However, no research has specifically reported the prevalence, species distribution, or associated factors of oral fungal infection in patients with HNC. Existing evidence indicates that CCRT for HNC substantially increases the risk of OC, and fungal-related mucosal damage may negatively affect oral health and QoL in this population. These gaps underscore the need for focused investigation. Accordingly, this study was conducted with the following objectives:

1. *To determine the prevalence of oral fungal infection, species distribution, and associated factors in patients with head and neck cancer.*
2. *To assess the impact of oral fungal infection on the quality of life of head and neck cancer patients undergoing concurrent chemoradiotherapy.*

2. Novel contributions of the thesis

- This study is among the few conducted in Vietnam that systematically investigate the prevalence of oral fungal infections among patients with HNC, thereby providing important epidemiological evidence regarding the burden of oral fungal infections in this high-risk population.

- The study employed a combination of morphological and molecular methods for fungal identification and reported several yeast species isolated from patients and documented for the first time in Vietnam. These findings broaden current

understanding of the diversity of pathogenic microorganisms in the oral cavity of cancer patients and have important scientific significance as well as practical implications for diagnosis, treatment, and epidemiological surveillance.

- The study also revealed that CCRT is strongly associated with oral fungal infections in patients with HNC, likely through alterations in the oral microbiological and immune environment, thereby increasing the risk of fungal infection. These findings provide a scientific basis for informing preventive strategies, early detection, and the management of oral fungal infections in patients before, during, and after chemoradiotherapy.

- This study is the first in Vietnam to evaluate the impact of oral fungal infections on the QoL of patients with HNC using a combination of internationally validated instruments, namely the EORTC QLQ-C30 and QLQ-HN43. These findings contribute to the development of comprehensive supportive care strategies in the management of HNC.

3. Structure of the dissertation

The dissertation comprises 143 pages, including: Introduction (2 pages), Literature Review (34 pages), Study Subjects and Methods (28 pages), Results (42 pages), Discussion (34 pages), Conclusions (2 pages), and Recommendations (1 page). It contains 38 tables, 13 images, 9 figures, and references to 222 documents. Two peer-reviewed articles directly related to the dissertation have been published.

Chapter 1

LITERATURE REVIEW

1.1. Overview of Head and Neck Cancer

1.1.1. Global and national epidemiology

HNC is a term used to describe a group of malignant tumors arising from the epithelium of the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, and salivary glands. It is the seventh most common malignancy worldwide and is associated with a high mortality rate, particularly in developing countries. Globally, HNC accounts for more than 890,000 new cases and approximately 450,000 deaths annually. The incidence of HNC is markedly higher in men than in women, with a male-to-female ratio ranging from 2:1 to 4:1. In Vietnam, nasopharyngeal carcinoma is the most prevalent subtype, accounting for approximately 33% of all HNC cases. In Ho Chi Minh city, the incidence of HNC has shown an increasing trend in both sexes, with men remaining predominant, representing about 73% of cases.

1.1.2. Risk factors

Risk factors for HNC include tobacco smoking and alcohol consumption; viral infections (human papillomavirus, particularly HPV-16, and Epstein–Barr virus); occupational and environmental exposures (such as wood dust, chemical agents, and air pollution); dietary patterns characterized by low intake of fruits and vegetables, vitamin deficiencies, and consumption of salted or fermented foods; poor oral hygiene and chronic inflammation; as well as individual factors including advanced age, male sex, and a positive family history.

1.1.3. Diagnosis and treatment of HNC

1.1.3.1. Clinical presentation

HNC commonly presents with persistent local symptoms, including non-healing oral ulcers, sore throat, hoarseness, dysphagia, or odynophagia. Patients may also

develop painless tumors or cervical lymphadenopathy that gradually increase in size over time. In addition, other symptoms such as oral or nasal bleeding, halitosis, facial numbness, or unexplained weight loss are frequently observed. In advanced stages, the disease may lead to malnutrition and significantly impair QoL.

1.1.3.2. Paraclinical investigations

- On endoscopic examination, HNC typically presents as exophytic masses, ulcerative or infiltrative lesions, or areas of abnormal mucosal thickening, which are friable, prone to bleeding on contact, and characterized by irregular margins. Depending on the tumor location, these lesions may result in narrowing or obstruction of the upper airway or upper digestive tract.

- From a histopathological perspective, the majority of cases are squamous cell carcinomas with varying degrees of differentiation.

- Additional study may reveal abnormalities in biochemical, hematological, or microbiological parameters, depending on the stage and extent of the disease.

1.1.3.3. Treatment of HNC

Treatment modalities for HNC include surgery, radiotherapy, and chemotherapy, which may be used alone or in combination depending on the tumor stage and location. Among these approaches, CCRT is commonly applied in patients without distant metastasis. In addition, targeted therapy and immunotherapy have emerged as promising strategies for the management of recurrent or metastatic HNC, aiming to improve treatment efficacy and patient prognosis.

1.1.4. Adverse effects of cancer treatment

Radiotherapy and chemotherapy in the treatment of HNC are frequently associated with a range of adverse effects, particularly within the irradiated fields. Common toxicities include oral and oropharyngeal mucositis, xerostomia resulting from salivary gland damage, taste disturbances, and dysphagia. Chemotherapy may also cause immunosuppression, anemia, nausea, vomiting, and generalized fatigue. Both radiotherapy and chemotherapy increase the risk of infections, especially oral fungal infections, which can exacerbate pain and swallowing difficulties, thereby significantly impairing patients' nutritional status and QoL.

1.2. Oral fungal infection and fungus-related oral lesions

1.2.1. Etiology and fungal lesions of the oral cavity

Oral fungal lesions are identified by the presence of fungal organisms in conjunction with clinical manifestations such as pain, erythema, ulceration, and white plaques within the oral cavity. To date, *C. albicans* remains the primary causative pathogen of OC. However, in recent years, non-*albicans Candida* species have shown an increasing trend in prevalence.

1.2.2. Prevalence and risk factors of oral fungal infection

- * *Prevalence of OC in cancer patients:* In HNC patients, OC is clearly associated with radiotherapy. A study by Jham et al. demonstrated that the prevalence of oral *Candida* spp. infection increased from 7.2% before radiotherapy to 21.1% after radiotherapy. Similarly, another study by Lalla et al. reported a statistically significant increase in the prevalence of OC in HNC patients, rising from 48.2% before treatment to 72.2% during treatment and 70.1% after treatment.

- * *Risk factors for Candida infection:* Risk determinants include environmental conditions within the oral cavity, local factors that disrupt mucosal integrity, and systemic factors affecting host immunity.

* *Causative species of Candida in oral infection: Candida albicans* accounts for more than 80% of pathogenic yeasts isolated from the oral cavity. However, the frequency of non-*C. albicans* species has been increasing in recent years.

1.2.3. Prevention and treatment of oral fungal infection

1.2.3.1. Treatment of OC

The treatment of OC should focus on two main objectives: (1) eradication or control of fungal infection within the oral cavity, and (2) identification and elimination of predisposing factors. Topical treatment options include nystatin in solution or gel formulations, miconazole gel or lozenges, and the use of adjunctive mouth rinses. For systemic therapy, fluconazole is generally considered the first-line agent, with the dosage and duration tailored according to disease severity and the patient's clinical condition.

1.2.3.2. Preventive measures

As OC is an opportunistic infection, preventive strategies primarily focus on minimizing predisposing factors that facilitate fungal overgrowth. In cancer patients, particularly those undergoing radiotherapy and/or chemotherapy, the appropriate use of antibiotics and corticosteroids with correct indications and dosages, along with close clinical monitoring during treatment to enable early detection of oral lesions, is essential. These measures should be combined with proper oral hygiene practices and interventions aimed at improving patients' overall nutritional and functional status.

1.3. Assessment of QoL in patients with HNC

1.3.1. Concept of QoL

The WHO defines "QoL" as individuals' perceptions of their position in life within the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns. Because health plays a pivotal role in determining QoL, the WHO has introduced the concept of "health-related QoL" (HRQoL) in the medical field. This concept encompasses all aspects of an individual's health, including both physical and mental well-being, that are closely related to and have a direct impact on overall QoL.

1.3.2. QoL assessment tools for patients with HNC

Analysis of the HaNDLE-on-QoL database indicates that more than 250 instruments have been used to assess QoL in patients with HNC, among which the most commonly employed are the QLQ-C30, QLQ-HN35, and the UW-QoL. The QLQ-C30 is a generic 30-item questionnaire that is widely used to evaluate QoL in cancer patients, whereas the QLQ-HN35 is a HNC –specific module, and the QLQ-HN43 represents an updated version designed to enhance comprehensiveness and measurement accuracy. The European Organisation for Research and Treatment of Cancer (EORTC) recommends combining disease-specific modules with the QLQ-C30 to ensure a comprehensive assessment of QoL. In Vietnam, most studies have employed the QLQ-C30 in combination with the QLQ-HN35 to assess QoL in patients with HNC; however, the application of the QLQ-HN43 in this population has not yet been reported.

1.4. Global and Vietnamese studies related to the research topic

1.4.1. International research

* *Oral fungal infection in patients with HNC:*

The prevalence of OC in patients with HNC receiving radiotherapy or CCRT

varies widely, ranging from 37% to 77%, with radiotherapy identified as an independent risk factor. The incidence of fungal infection tends to increase markedly during the course of treatment, rising from approximately 26% prior to radiotherapy to over 60% during radiotherapy, and is significantly higher in patients undergoing CCRT compared with those receiving radiotherapy alone. Factors such as sex, diabetes mellitus, smoking, alcohol consumption, and tumor location appear to be less strongly associated with fungal infection. Regarding etiology, *C. albicans* remains the predominant species; however, non-*C. albicans* species has been increasing, which is clinically relevant due to their higher potential for antifungal resistance.

** Impact of CCRT on QoL of patients with HNC:*

The QoL of patients with HNC is substantially affected during CCRT due to both acute and chronic adverse effects, including mucositis, xerostomia, swallowing disorders, taste impairment, and fatigue, leading to deterioration across physical, psychological, and social domains. Studies employing the QLQ-C30 together with the QLQ-HN35 or QLQ-HN43 instruments have consistently reported a marked decline in QoL during the active treatment phase. Although some aspects improve over time, many persistent symptoms remain long term. Pretreatment QoL - particularly global health status and physical functioning - has been shown to be closely associated with post-treatment survival outcomes. Intensity-modulated radiotherapy has demonstrated the potential to improve QoL scores compared with other radiotherapy techniques; however, QoL still declines significantly following treatment and only gradually recovers after 6–12 months. In some long-term survivors, conditions such as xerostomia, impaired physical functioning, and taste disturbances may persist for many years after treatment.

** Impact of oral fungal infection on QoL of patients with HNC*

Oral *Candida* infection may exacerbate chemoradiotherapy-induced mucositis, resulting in pain, difficulty in eating and swallowing, and consequently leading to malnutrition, weight loss, and physical debilitation. The presence of *Candida*, together with oral symptoms such as pain, xerostomia, ulceration, and taste disturbances, has a profound negative impact on the QoL of patients with HNC.

1.4.2. Research in Vietnam

** Oral fungal infection in cancer patients*

Mai Anh Loi et al. (2017) reported an OC prevalence of 43.07% among cancer patients; this condition was associated with radiotherapy, receiving more than three cycles of chemotherapy, and hypoalbuminemia. However, the study did not assess patients' QoL. A study by Ton Nu Phuong Anh et al. (2023) showed that 45.8% of patients undergoing cancer treatment developed OC, with *C. albicans* accounting for 70.9% of cases; notably, the prevalence was significantly higher in the chemotherapy group (65.8%) compared with patients who did not receive chemotherapy (35.4%). Nevertheless, this study did not provide data specific to patients with HNC. Nguyen et al. (2024), in a study of nasopharyngeal cancer patients treated with radiotherapy and/or chemotherapy, identified *C. albicans* as the predominant species (63.16%), followed by *C. glabrata*, *C. tropicalis*, and *C. krusei*. The rates of resistance to fluconazole, clotrimazole, and miconazole among these species were 85.71%, 53.57%, and 57.14%, respectively, which were higher than those observed for *C. albicans*. However, this study did not evaluate factors associated with OC.

** QoL assessment in patients with HNC*

In Vietnam, several studies have assessed the QoL of patients with HNC, primarily using the QLQ-C30 and QLQ-HN35 instruments; however, they have not specifically analyzed the impact of cancer treatment and oral fungal infections on QoL. Domestic data on oral Candida infections among HNC patients remain limited, with existing studies mainly describing prevalence rates, species distribution, and antifungal susceptibility profiles. To date, no studies have evaluated factors associated with OC or its direct impact on the QoL of HNC patients, particularly among those receiving CCRT. The limited number of available studies also hampers meaningful synthesis and comparison of findings. Therefore, further in-depth investigations are warranted to elucidate the relationships between OC, treatment modalities, and QoL, thereby informing comprehensive care strategies and improving QoL outcomes for patients with HNC.

Chapter 2

STUDY SUBJECTS AND METHODS

2.1. Study population, setting, and study period

Participants were patients aged 18 years or older diagnosed with HNC based on histopathological confirmation.

2.1.1. Inclusion criteria

- Patients with histopathologically confirmed HNC, with tumor staging determined according to the AJCC 8th edition.
- Indicated for CCRT.
- Underwent diagnostic testing for oral fungal infection with definitive results.
- Age ≥ 18 years and cognitively capable of understanding and completing survey questionnaires.
- Provided informed consent to participate in the study.

2.1.2. Exclusion criteria

- HNC with distant metastasis.
- Concurrent diagnosis of another malignancy.
- Incomplete or unclear medical records.
- Use of systemic or topical antifungal agents within 2 weeks prior to clinical assessment and sample collection.
- Severe immunosuppression (e.g., HIV/AIDS).
- Declined to participate in the study.

2.1.3. Study setting and study period

Study sites:

- Clinical examination and sample collection were conducted at 103 Military Hospital, 108 Military Central Hospital, Hanoi Oncology Hospital and National Hospital of Otorhinolaryngology
- Fungal testing and species identification were performed at the Department of Parasitology and Entomology, Military Medical University.

Study period: December 2020 to December 2024.

2.2. Study components

- To determine the prevalence of oral fungal infections, species distribution, and selected factors associated with OC in patients with HNC.
- To evaluate the impact of OC on the QoL of HNC patients undergoing CCRT.

2.3. Research methods

2.3.1. Study design: A cross-sectional descriptive study with analytical components.

2.3.2. Sample size and sampling method

Sample size: The sample size for estimating the prevalence of oral fungal infection in patients with HNC was calculated using the following formula:

$$n = Z_{1-\alpha/2}^2 \times \frac{p(1-p)}{d^2}$$

Where: $p = 0.43$ (based on the study by Mai Anh Lợi et al.), $d = 0.08$ and at a 95% confidence level, $Z_{1-\alpha/2}^2 = 1.96$. Substituting these values yields a minimum required sample size of $n = 147$. In practice, 156 HNC patients meeting the inclusion criteria were enrolled, including: 41 patients from 103 Military Hospital, 45 from 108 Military Central Hospital, 33 from Hanoi Oncology Hospital, and 37 from the National Hospital of Otorhinolaryngology.

Sampling method and data collection: A convenience sampling approach was used. At each participating hospital, all eligible patients were consecutively recruited until the required sample size was achieved.

2.4. Techniques and procedures used in the study

The study collected participant information using standardized case report forms, in combination with clinical examinations and oral rinse sampling to assess oral fungal infection status. Oral fungal infection was determined by direct microscopic examination and culture on ChromAgar™ Candida medium, along with the performance of relevant laboratory investigations. Patients received CCRT according to standard treatment protocols, including radiotherapy delivered using a linear accelerator and cisplatin-based chemotherapy administered in standard cycles. Fungal species were identified using PCR–RFLP and sequencing of the internal transcribed spacer (ITS) region. The QoL of HNC patients was evaluated using the QLQ-C30 and QLQ-HN43 questionnaires in accordance with EORTC guidelines.

2.5. Study variables and indexes

2.5.1. Study variables

The study collected general patient information, including demographic characteristics, lifestyle habits, oral hygiene status, and comorbidities. Clinical characteristics recorded comprised the site and type of HNC, lymph node metastasis status, disease stage, weight loss, receipt of CCRT, oral mucosal lesions, and the fungal species isolated. Paraclinical parameters, including red blood cell count, white blood cell count, hemoglobin concentration, and blood glucose levels, were also assessed. Patients' general performance status was evaluated using the Karnofsky Performance Status scale. QoL was assessed across functional domains, symptom domains, financial difficulties, and overall/global health status.

2.5.2. Research indices

- Prevalence of oral fungal infection; prevalence of clinically evident OC.
- Proportion of each fungal species; rate of single-species versus co-infection.
- Severity of oral mucositis according to WHO (1979) criteria.
- Classification of key hematological and biochemical indices.
- Karnofsky Performance Status (KPS) score.

2.6. Data processing and statistical analysis

Research data were entered and analyzed using IBM SPSS software V.22.0.

2.7. Ethical considerations

The study was reviewed and approved by the Institutional Review Board of 103 Military Hospital, with Ethics Approval Certificate No. 181/2021/CNChT-HĐĐĐ dated August 10, 2021.

Chapter 3 RESULTS

3.1. General characteristics of the study population

In this study, the majority of patients with HNC were male and older than 40 years. Most participants belonged to the Kinh ethnic group (96.79%) and were predominantly engaged in agriculture (27.56%), retired civil servants (21.15%), or self-employed/other occupational groups (29.49%). In addition, 66.03% of patients had attained an educational level of high school or higher. Squamous cell carcinoma and undifferentiated carcinoma accounted for 69.87% of all cases, whereas other histological types were less common, with proportions ranging from 3.2% to 10.90%. Regarding disease stage, stage IV was the most prevalent (44.23%), followed by stage III (32.05%), stage II (21.16%), and stage I (2.56%).

3.2. Oral fungal infection, species distribution, and associated factors in patients with HNC

3.2.1. Characteristics of oral fungal infection in HNC patients

Among the 156 patients with HNC, 82 patients (52.56%) were identified as having fungal presence in the oral cavity, and all isolated strains belonged to the yeast group. Within this group of patients with fungal presence, 75 cases (accounting for 48.08% of the total study population) exhibited oral mucosal lesions attributable to yeast infection.

In HNC patients, the most frequent oral fungal lesions were white plaques (36.0%), followed by angular cheilitis (30.7%), fissured tongue (14.7%), mucosal bleeding (8.0%), and ulcerations (2.7%). Other lesion types comprised 48.0% of cases.

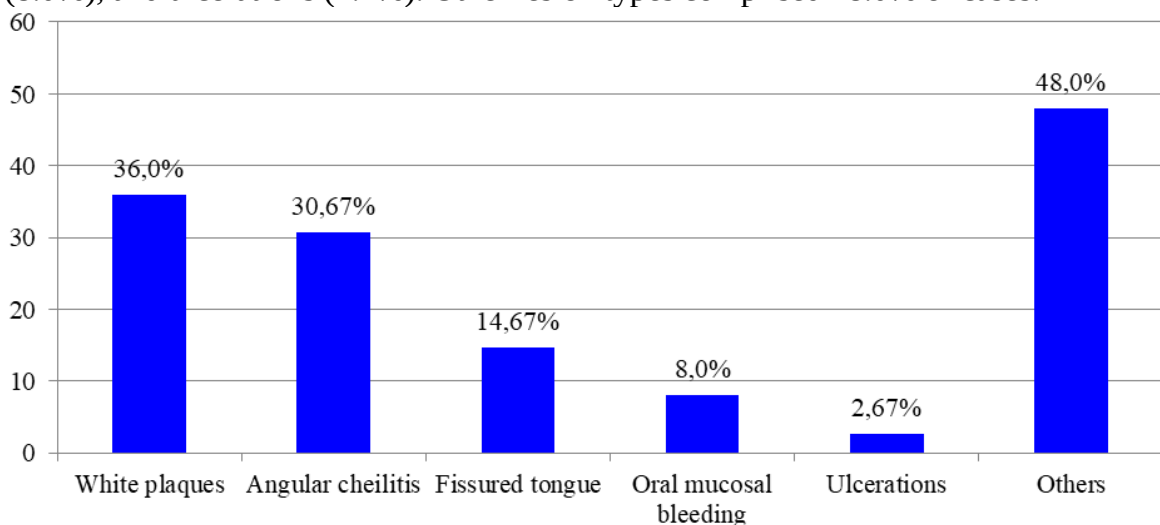


Figure 3.1. Types of oral lesions associated with yeast infections among patients with HNC

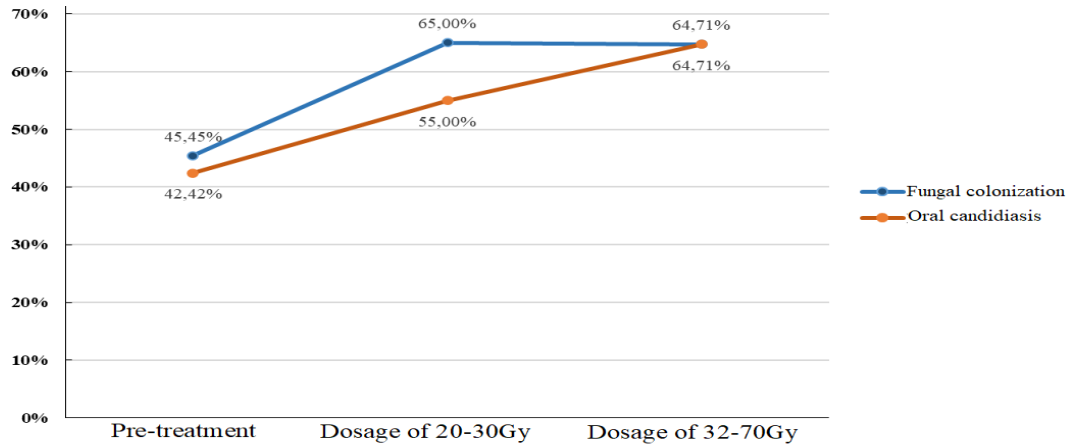


Figure 3.2. Distribution of oral fungal colonization and infection in HNC patients by timing of CCRT.

In this study, the results showed that the incidence of oral fungal colonization and infection in HNC patients increased significantly following CCRT.

Table 3.1. Oral mucositis in patients with oral fungal infection by CCRT (n = 75)

Grade of oral mucositis	CCRT (No, %)		Total
	No	Yes	
Grade 0	31 (73,81)	2 (6,06)	33 (44,0)
Grade I	10 (23,81)	14 (42,42)	24 (32,0)
≥ Grade II	1 (2,38)	17 (51,52)	18 (24,0)
Total	42 (100)	33 (100)	75 (100)
χ^2, p_{1-2}	$\chi^2 = 39,88; p < 0,001$		

The severity of oral mucositis was significantly higher in patients with oral fungal infections who received CCRT, compared to those who did not. Patients without CCRT exhibited notably lower levels of mucositis. This difference was statistically significant ($p < 0.001$).

3.2.2. Species composition of yeasts isolated from the oral cavity of patients with HNC

Table 3.2. Pattern of oral fungal single -infection and co-infection in HNC patients

Status	No	%	Loại nấm	No	%
Single infection	73	89.02	<i>C. albicans</i>	53	64.63
			<i>C. africana</i>	1	1.22
			<i>C. dubliniensis</i>	1	1.22
			<i>C. tropicalis</i>	2	2.44
			<i>C. glabrata</i>	3	3.66
			<i>C. ethanolica</i>	1	1.22
			<i>C. parapsilosis</i>	6	7.31
			<i>C. mesorugosa</i>	1	1.22
			<i>Kodame ohmeri</i>	3	3.66
			<i>S. cerevisiae</i>	1	1.22
			<i>Pichia kluyveri</i>	1	1.22
Co-infection	9	10.98	<i>C. albicans</i> và <i>C. tropicalis</i>	4	4.88
			<i>C. albicans</i> và <i>C. glabrata</i>	1	1.22
			<i>C. tropicalis</i> và <i>C. intermedia</i>	2	2.44
			<i>C. albicans</i> , <i>C. tropicalis</i> và <i>M. caribbica</i>	1	1.22
			<i>C. tropicalis</i> , <i>C. quercitrusa</i> , <i>Wi. anomalus</i> và <i>Debaryomyces nepalensis</i>	1	1.22
Total	82	100	Total	82	100

Among the 82 patients with HNC and oral fungal infection, 73 patients (89.02%) were infected with a single fungal species, including *C. albicans*, *C. africana*, *C. dubliniensis*, *C. tropicalis*, *C. glabrata*, *C. ethanolica*, *C. parapsilosis*, *K. ohmeri*, *S. cerevisiae*, and *P. kluyveri*. Co-infection was identified in 9 cases (10.98%), 4 cases of co-infection with *C. albicans* and *C. tropicalis*, 2 cases with *C. tropicalis* and *C. intermedia*, 1 case with *C. tropicalis* and *C. glabrata*, 1 case with triple co-infection involving *C. albicans*, *C. tropicalis*, and *M. caribbica*, and 1 case with quadruple co-infection involving *C. tropicalis*, *C. quercitrusa*, *W. anomalus*, and *D. nepalensis*.

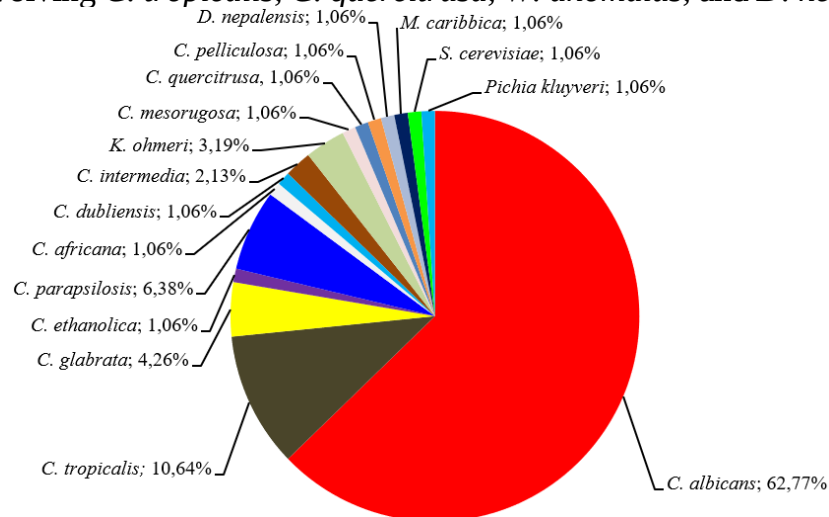


Figure 3.3. Distribution of fungal species isolated from the oral cavity of patients with HNC.

A total of 94 yeast isolates were obtained from 82 oral cavity samples. Based on species identification using CHROMagar™ Candida, PCR–RFLP, and sequencing analysis, 16 different fungal species were identified. *C. albicans* was the most prevalent species (59 isolates; 62.77%), followed by *C. tropicalis* (10 isolates; 10.64%), *C. parapsilosis* (6 isolates; 6.38%), *C. glabrata* (4 isolates; 4.26%), *K. ohmeri* (3 isolates; 3.19%), and *C. intermedia* (2 isolates; 2.13%). The remaining species included *C. africana*, *C. dubliniensis*, *C. ethanolica* (also known as *Pichia ethanolica*), *C. mesorugosa*, *C. quercitrusa* (also known as *Kurtzmaniella quercitrusa*), *C. pelliculosa* (also known as *W. anomalus*), *D. nepalensis*, *M. caribbica*, *S. cerevisiae*, and *P. kluyveri*, each represented by a single isolate (1.06%).

3.2.3. Factors associated with oral fungal infection in patients with HNC

Table 3.3. Association between oral fungal colonization and demographic, medical history, and clinical factors among patients with HNC (n = 156)

[illegible]

Characteristics	N	n (Pos)	% (Pos)	Univariate analysis		Multivariate analysis	
				OR (95%CI)	p	OR (95%CI)	p
≤ Secondary school	53	32	60,38	1,62 (0,82 – 3,17)	0,161		
≥ High school	103	50	48,54	1			
Occupation							
Farmer and worker	48	28	58,33	1,40 (0,71 – 2,78)	0,336		
Others	108	54	50,00	1			
Smoking							
Yes	74	35	47,30	0,67 (0,36 – 1,26)	0,211		
No	82	47	57,32	1			
The use any antibiotics within one month							
Yes	53	25	47,17	0,72 (0,37 – 1,40)	0,334		
No	103	57	55,34	1			
Diabetes mellitus							
Yes	19	12	63,16	1,64 (0,61 – 4,42)	0,324		
No	137	70	51,09	1			
Oral hygiene routine							
Yes	10	5	50,0	0,90 (0,25 – 3,23)	0,867		
No	146	77	52,74	1	1		
Denture wearer							
Yes	24	13	54,17	1,08 (0,45 – 2,58)	0,864		
No	132	69	52,27	1			
Anatomic stage							
Stage IV	69	38	55,07	1,20 (0,64 – 2,26)	0,576		
Stage ≤ III	87	44	50,57	1			
Lymph node metastases							
Yes	110	55	50,0	0,70 (0,35 – 1,41)	0,321		
No	46	27	58,69	1			
CCRT							
Yes	57	37	64,91	2,22 (1,13 – 4,35)	0,019	2,07 (1,05 – 4,09)	0,037
No	99	45	45,45	1		1	
Type of cancer							
SCC*	78	36	46,15	0,60 (0,32 – 1,12)	0,109		
others	78	46	58,97	1			
Weight loss							
Yes	95	56	58,95	1,93 (1,01 – 3,71)	0,046	1,77 (0,91 – 3,45)	0,091
No	61	26	42,62	1		1	

*SCC: Squamous Cell Carcinoma

Based on the univariate analysis, two factors were found to be associated with an increased risk of oral fungal colonization: CCRT (OR = 2.22; 95% CI: 1.13–4.35; p = 0.019) and weight loss (OR = 1.93; 95% CI: 1.01–3.71; p = 0.046). However, multivariate analysis revealed that only CCRT remained a significant risk factor for oral fungal colonization among patients with HNC.

3.3. Impact of oral fungal infection on QoL in HNC patients undergoing CCRT

3.3.1. QoL outcomes using the QLQ-C30

Table 3.4. Comparison of QoL between hnc patients with and without oral fungal infection using the QLQ-C30

Variables	Fungal infection (n = 82)		No fungal infection (n = 74)		p*
	$\bar{X} \pm SD$	M	$\bar{X} \pm SD$	M	
Functional domains					
Physical functioning	89.67 ± 15.82	100	90.18 ± 13.43	100	0.814
Role functioning	86.21 ± 21.86	100	86.71 ± 19.89	100	0.854
Emotional functioning	86.89 ± 18.52	91.67	84.23 ± 19.14	91.67	0.489
Cognitive functioning	90.45 ± 15.94	100	90.09 ± 16.07	100	0.896
Social functioning	84.35 ± 23.03	100	82.88 ± 19.70	83.33	0.315
Symptom domains					
Fatigue	21.54 ± 22.45	11.11	21.77 ± 22.56	22.22	0.921
Nausea/vomiting	9.15 ± 18.36	0	10.36 ± 16.71	0	0.379
Pain	17.68 ± 21.81	8.33	15.77 ± 20.06	0	0.686
Dyspnea	6.50 ± 16.09	0	5.40 ± 12.37	0	0.969
Insomnia	17.89 ± 26.29	0	21.17 ± 31.49	0	0.637
Appetite loss	26.75 ± 30.92	0	23.42 ± 27.99	33.33	0.613
Constipation	8.54 ± 18.75	0	13.06 ± 21.94	0	0.135
Diarrhea	4.88 ± 14.93	0	8.56 ± 16.61	0	0.057
Financial difficulties	21.54 ± 30.71	0	29.28 ± 28.64	33.33	0.035
Global health status	63.62 ± 19.27	66.67	61.49 ± 21.09	66.67	0.424

Across global health status, functional scales, and symptom scales, no significant differences were observed between patients with and without oral fungal infection. In contrast, financial difficulty scores differed significantly, with higher financial burden reported in the group without oral fungal infection ($p = 0.035$).

Table 3.5. Comparison of QoL between HNC patients with and without OC using the QLQ-C30

Variables	With OC (n = 75)		Without OC (n = 81)		<i>p</i> *
	$\bar{X} \pm \text{SD}$	M	$\bar{X} \pm \text{SD}$	M	
Functional domains					
Physical functioning	89.33 ± 16.29	100	90.45 ± 13.12	100	0.923
Role functioning	85.59 ± 22.12	100	87.24 ± 19.77	100	0.788
Emotional functioning	86.44 ± 19.17	91.67	84.88 ± 18.55	91.67	0.546
Cognitive functioning	90.44 ± 16.02	100	90.12 ± 15.98	100	0.923
Social functioning	84.00 ± 23.80	100	83.33 ± 19.18	83.33	0.350
Symptom domains					
Fatigue	22.37 ± 22.70	22.22	20.99 ± 22.29	22.22	0.583
Nausea/vomiting	8.44 ± 17.62	0	10.91 ± 17.51	0	0.202
Pain	18.22 ± 22.46	0	15.43 ± 19.50	0	0.606
Dyspnea	6.67 ± 16.44	0	5.35 ± 12.31	0	0.920
Insomnia	16.89 ± 25.92	0	21.81 ± 31.25	0	0.361
Appetite loss	26.58 ± 31.20	0	23.87 ± 28.01	33.33	0.738
Constipation	8.44 ± 19.06	0	12.76 ± 21.45	0	0.126
Diarrhea	4.89 ± 15.20	0	8.23 ± 16.27	0	0.069
Financial difficulties	22.67 ± 31.08	0	27.57 ± 28.77	33.33	0.152
Global health status	64.00 ± 19.58	66.67	61.32 ± 20.64	66.67	0.272

* Mann–Whitney test; : mean; SD: standard deviation; M: median.

QoL scores did not differ significantly between patients with and without OC across the four assessed domains: functional scales, symptom burden, financial difficulties, and global health status.

Table 3.6. Comparison of QoL between HNC patients with and without CCRT using the QLQ-C30 scale

Variables	Received CCRT (n = 57)		Not received CCRT (n = 99)		<i>p</i> *
	$\bar{X} \pm \text{SD}$	M	$\bar{X} \pm \text{SD}$	M	
Functional domains					
Physical functioning	83.86 ± 17.73	86.67	94.40 ± 11.33	100	< 0.001
Role functioning	80.99 ± 22.81	83.33	89.80 ± 19.07	100	0.004
Emotional functioning	79.82 ± 20.41	91.67	85.57 ± 17.04	100	< 0.001
Cognitive functioning	88.30 ± 18.08	100	91.41 ± 14.55	100	0.386
Social functioning	81.87 ± 23.21	83.33	84.68 ± 20.44	100	0.437
Symptom domains					
Fatigue	32.36 ± 24.51	33.33	15.49 ± 18.63	11.11	< 0.001
Nausea/vomiting	17.84 ± 22.02	0	5.05 ± 12.25	0	< 0.001
Pain	28.95 ± 23.68	33.33	9.76 ± 15.43	0	< 0.001
Dyspnea	8.19 ± 18.13	0	4.71 ± 11.67	0	0.336
Insomnia	26.90 ± 33.59	0	15.15 ± 24.87	0	0.031
Appetite loss	48.54 ± 28.92	33.33	11.56 ± 19.79	0	< 0.001
Constipation	12.87 ± 21.60	0	9.48 ± 19.66	0	0.222
Diarrhea	8.19 ± 17.00	0	5.72 ± 15.09	0	0.277
Financial difficulties	23.98 ± 31.34	0	25.93 ± 29.18	33.33	0.538
Global health status	58.92 ± 23.77	66.67	64.73 ± 17.45	66.77	0.355

* Mann–Whitney test; : mean; SD: standard deviation; M: median.

Statistically significant differences were observed between the two groups across several functional domains, including physical, role, and emotional functioning, as well as in key symptom domains such as fatigue, nausea/vomiting, pain, insomnia, and appetite loss ($p < 0.05$). CCRT was associated with greater impairments in these QoL domains.

Table 3.7. Comparison of QoL between HNC patients receiving chemoradiotherapy with and without oral fungal infection using the QLQ-C30

Variables	CCRT with fungal infection (n = 37)		CCRT without fungal infection (n = 20)		p*
	$\bar{X} \pm \text{SD}$	M	$\bar{X} \pm \text{SD}$	M	
Functional domains					
Physical functioning	83.06 ± 19.66	86.67	85.33 ± 13.78	86.67	0.959
Role functioning	79.73 ± 24.58	83.33	83.33 ± 19.50	83.33	0.796
Emotional functioning	81.08 ± 19.90	91.67	75.50 ± 21.65	87.50	0.617
Cognitive functioning	87.39 ± 19.41	100	90.00 ± 15.67	100	0.798
Social functioning	80.63 ± 26.50	100	84.17 ± 15.74	83.33	0.921
Symptom domains					
Fatigue	31.53 ± 23.79	33.33	33.89 ± 26.36	22.22	1
Nausea/vomiting	17.12 ± 23.73	0	19.17 ± 18.95	25.00	0.544
Pain	29.73 ± 23.94	33.33	27.50 ± 23.74	16.67	0.783
Dyspnea	9.91 ± 20.59	0	5.00 ± 12.21	0	0.480
Insomnia	24.32 ± 30.07	0	31.67 ± 39.70	16.67	0.609

Variables	CCRT with fungal infection (n = 37)		CCRT without fungal infection (n = 20)		p*
	$\bar{X} \pm SD$	M	$\bar{X} \pm SD$	M	
Appetite loss	47.75 $\pm$ 28.91	66.67	50.00 $\pm$ 29.62	33.33	0.908
Constipation	12.61 $\pm$ 22.71	0	13.33 $\pm$ 19.94	0	0.719
Diarrhea	8.10 $\pm$ 18.27	0	8.33 $\pm$ 14.81	0	0.680
Financial difficulties	20.72 $\pm$ 30.78	0	30.00 $\pm$ 32.26	33.33	0.190
Global health status	62.39 $\pm$ 22.53	66.67	52.50 $\pm$ 25.23	50.00	0.141

* Mann–Whitney test; : mean; SD: standard deviation; M: median.

Across all domains of the QLQ-C30, no statistically significant differences were observed between patients with oral fungal infection and those without infection among the subgroup receiving CCRT ($p > 0.05$).

Table 3.8. Comparison of QoL between HNC patients without chemoradiotherapy with and without oral fungal infection using the QLQ-C30

Variables	No CCRT + fungal infection (n = 45)		No CCRT + no fungal infection (n = 54)		p*
	$\bar{X} \pm \text{SD}$	M	$\bar{X} \pm \text{SD}$	M	
Functional domains					
Physical functioning	95.11 ± 8.81	100	91.98 ± 12.98	100	0.309
Role functioning	91.67 ± 17.79	100	87.96 ± 20.07	100	0.264
Emotional functioning	91.67 ± 15.99	100	86.73 ± 17.70	100	0.119
Cognitive functioning	92.96 ± 12.04	100	90.12 ± 16.36	100	0.576
Social functioning	87.41 ± 19.51	100	82.41 ± 21.09	91.67	0.188
Symptom domains					
Fatigue	13.33 ± 17.66	0	17.28 ± 19.39	16.67	0.319
Nausea/vomiting	2.59 ± 7.91	0	7.10 ± 14.70	0	0.117
Pain	7.78 ± 13.58	0	11.42 ± 16.77	0	0.273
Dyspnea	3.70 ± 10.59	0	5.56 ± 12.54	0	0.432
Insomnia	12.59 ± 21.66	0	17.28 ± 27.27	0	0.409
Appetite loss	9.09 ± 19.51	0	13.58 ± 19.98	0	0.121
Constipation	5.19 ± 14.13	0	12.96 ± 28.82	0	0.049
Diarrhea	2.22 ± 11.01	0	8.64 ± 17.36	0	0.014
Financial difficulties	22.22 ± 30.98	0	29.01 ± 27.51	33.33	0.128
Global health status	64.63 ± 16.30	66.67	64.81 ± 18.50	66.67	0.940

* Mann–Whitney test; : mean; SD: standard deviation; M: median.

Within the functional domains, patients who did not receive chemoradiotherapy and had oral fungal infection demonstrated higher QoL scores than those without infection; however, these differences did not reach statistical significance. Across the eight symptom domains, patients with oral fungal infection exhibited poorer symptom scores, with statistically significant differences observed only for constipation and diarrhea ($p < 0.05$). No statistically significant differences were identified between the two groups with respect to financial difficulties or global health status.

Table 3.9. Comparison of QoL between HNC patients with oral fungal infection undergoing and not undergoing CCRT

Variables	CCRT + fungal infection (n = 37)		No CCRT + fungal infection (n = 45)		<i>p</i> *
	$\bar{X} \pm \text{SD}$	M	$\bar{X} \pm \text{SD}$	M	
Functional domains					
Physical functioning	83.06 ± 19.66	86.67	95.11 ± 8.81	100	0.002
Role functioning	79.73 ± 24.58	83.33	91.67 ± 17.79	100	0.008
Emotional functioning	81.08 ± 19.90	91.67	91.67 ± 15.99	100	< 0.001
Cognitive functioning	87.39 ± 19.41	100	92.96 ± 12.04	100	0.308
Social functioning	80.63 ± 26.50	100	87.41 ± 19.51	100	0.239
Symptom domains					
Fatigue	31.53 ± 23.79	33.33	13.33 ± 17.66	0	< 0.001
Nausea/vomiting	17.12 ± 23.73	0	2.59 ± 7.91	0	0.002
Pain	29.73 ± 23.34	33.33	7.78 ± 13.58	0	< 0.001
Dyspnea	9.91 ± 20.58	0	3.70 ± 10.59	0	0.163
Insomnia	24.32 ± 30.07	0	12.59 ± 21.66	0	0.067
Appetite loss	47.75 ± 28.91	66.67	9.09 ± 19.51	0	< 0.001
Constipation	12.61 ± 22.70	0	5.19 ± 14.13	0	0.069
Diarrhea	8.11 ± 18.27	0	2.22 ± 11.01	0	0.041
Financial difficulties	20.72 ± 30.78	0	22.22 ± 30.98	0	0.870
Global health status	62.39 ± 22.53	66.67	64.63 ± 16.30	66.67	0.894

* *Mann–Whitney test*; : mean; *SD*: standard deviation; *M*: median.

Patients with oral fungal infection who underwent CCRT experienced significantly poorer physical, role, and emotional functioning and a higher symptom burden—including fatigue, nausea/vomiting, pain, appetite loss, and diarrhea—than infected patients not yet treated ($p < 0.05$), while no significant differences were observed in global health status or financial difficulties.

3.3.2. Assessment of the impact of oral fungal infection on QoL in HNC patients undergoing CCRT using the QLQ-HN43 scale

Table 3.10. Comparison of QoL between HNC patients with and without oral fungal infection assessed using the QLQ-HN43

Variables	Fungal infection (n = 82)		No fungal infection (n = 74)		p*
	Mean ± SD	Median	Mean ± SD	Median	
Multi-item scales					
Dry mouth/thick saliva	23.58 ± 23.56	16.67	19.37 ± 23.56	16.67	0.180
Oral pain	11.79 ± 17.71	0	11.15 ± 14.94	0	0.794
Sensory problems	18.50 ± 26.32	0	13.29 ± 24.36	0	0.075
Social eating difficulties	16.77 ± 19.78	8.33	13.93 ± 19.40	0	0.208
Swallowing difficulties	16.56 ± 19.74	8.33	17.57 ± 23.87	8.33	0.876
Sexuality concerns	16.67 ± 24.98	0	16.89 ± 27.38	0	0.869
Body image concerns	14.43 ± 20.08	0	17.34 ± 22.15	0	0.469
Speech problems	15.53 ± 21.62	6.67	15.32 ± 20.61	6.67	0.769
Dental problems	9.62 ± 15.69	0	10.81 ± 16.03	0	0.741
Anxiety	27.24 ± 28.39	16.67	29.51 ± 29.14	33.33	0.630
Shoulder problems	9.96 ± 16.94	0	9.46 ± 17.90	0	0.762
Skin problems	12.74 ± 16.57	0	11.11 ± 19.81	0	0.194
Single-item scales					
Coughing	13.41 ± 20.19	0	16.67 ± 25.43	0	0.610

Variables	Fungal infection (n = 82)		No fungal infection (n = 74)		<i>p</i> *
	Mean $\pm$ SD	Median	Mean $\pm$ SD	Median	
Impaired mouth opening	9.35 $\pm$ 18.35	0	16.22 $\pm$ 24.82	0	0.075
Social contact difficulties	10.16 $\pm$ 20.75	0	15.77 $\pm$ 26.01	0	0.142
Neurological problems	10.16 $\pm$ 19.38	0	9.91 $\pm$ 17.21	0	0.816
Neck swelling	15.04 $\pm$ 23.51	0	13.06 $\pm$ 23.93	0	0.416
Concern about weight loss	20.16 $\pm$ 29.66	0	17.12 $\pm$ 24.20	0	0.818
Delayed wound healing	15.04 $\pm$ 24.65	0	15.32 $\pm$ 24.79	0	0.879

* *Mann–Whitney test*

No statistically significant differences were observed in QoL scores between patients with and without oral fungal infection across all QLQ-HN43 domains.

Table 3.11. Comparison of QoL between HNC patients with and without CCRT assessed using the QLQ-HN43

Variables	CCRT (n = 57)		No CCRT (n = 99)		<i>p</i> *
	Mean ± SD	Median	Mean ± SD	Median	
Multi-item scales					
Dry mouth/thick saliva	39.18 ± 23.25	33.33	11.45 ± 17.11	0	< 0.001
Oral pain	18.27 ± 19.82	16.67	7.58 ± 12.60	0	< 0.001
Sensory problems	29.24 ± 29.27	16.67	8.42 ± 18.80	0	< 0.001
Social eating difficulties	26.46 ± 20.11	25.0	9.01 ± 15.59	0	< 0.001
Swallowing difficulties	28.80 ± 22.61	25.0	10.20 ± 18.09	0	< 0.001
Sexuality concerns	22.81 ± 30.48	0	13.30 ± 22.59	0	0.045
Body image concerns	19.30 ± 23.10	16.67	13.81 ± 19.64	0	0.105
Speech problems	21.64 ± 24.18	13.33	11.85 ± 18.26	0	0.011
Dental problems	15.59 ± 19.34	11.11	7.07 ± 12.44	0	0.004
Anxiety	38.30 ± 28.86	33.33	22.56 ± 27.08	16.67	< 0.001
Shoulder problems	15.50 ± 18.86	0	6.40 ± 15.56	0	< 0.001
Skin problems	20.27 ± 18.80	22.22	7.18 ± 15.98	0	< 0.001
Single-item scales					
Coughing	20.47 ± 27.28	0	11.78 ± 19.23	0	0.046
Impaired mouth opening	16.96 ± 25.29	0	10.10 ± 19.32	0	0.109
Social contact difficulties	17.54 ± 25.28	0	10.10 ± 22.06	0	0.032
Neurological problems	16.96 ± 23.67	0	6.06 ± 12.92	0	0.002
Neck swelling	21.64 ± 24.79	33.33	9.76 ± 21.95	0	< 0.001
Concern about weight loss	31.57 ± 31.76	33.33	11.22 ± 20.83	0	< 0.001
Delayed wound healing	24.56 ± 28.54	33.33	9.76 ± 20.34	0	< 0.001

* *Mann–Whitney test*

CCRT was associated with significantly worse scores across nearly all QOL domains, except for body image concerns and difficulty opening the mouth.

Table 3.12. Comparison of QoL between HNC patients undergoing CCRT with and without oral fungal infection using the QLQ-HN43

Variables	CCRT + fungal infection (n = 37)		CCRT + no fungal infection (n = 20)		p*
	Mean ± SD	Median	Mean ± SD	Median	
Multi-item scales					
Dry mouth/thick saliva	40.09 ± 22.72	33.33	37.50 ± 24.71	33.33	0.542
Oral pain	19.37 ± 21.88	16.67	16.25 ± 15.64	16.67	0.938
Sensory problems	31.08 ± 29.70	16.67	25.83 ± 30.81	16.67	0.277

Social eating difficulties	27.25 ± 19.01	16.67	25.00 ± 22.46	25.00	0.548
Swallowing difficulties	27.93 ± 20.53	33.33	30.42 ± 26.53	25.00	0.987
Sexuality concerns	19.37 ± 27.64	0	29.17 ± 34.99	16.67	0.249
Body image concerns	19.82 ± 24.48	16.67	18.33 ± 20.87	16.67	0.944
Speech problems	22.34 ± 25.49	13.33	20.33 ± 22.11	16.67	0.952
Dental problems	14.41 ± 19.04	11.11	17.78 ± 20.20	11.11	0.608
Anxiety	38.74 ± 25.51	33.33	37.50 ± 31.93	33.33	0.680
Shoulder problems	14.41 ± 19.71	0	17.50 ± 17.50	16.67	0.377
Skin problems	21.02 ± 18.10	22.22	18.89 ± 20.42	11.11	0.571
Single-item scales					
Coughing	17.12 ± 23.07	0	26.67 ± 33.51	16.67	0.378
Impaired mouth opening	12.61 ± 21.30	0	25.00 ± 30.35	0	0.133
Social contact difficulties	14.41 ± 24.27	0	23.33 ± 26.71	16.67	0.160
Neurological problems	16.22 ± 24.37	0	18.33 ± 22.88	0	0.602
Neck swelling	22.52 ± 24.91	33.33	20.00 ± 25.13	0	0.672
Concern about weight loss	35.14 ± 32.28	33.33	25.00 ± 28.36	33.33	0.275
Delayed wound healing	25.23 ± 29.82	0	23.33 ± 26.71	33.33	0.935

* *Mann–Whitney test*

There were no statistically significant differences across any QoL domains between patients receiving CCRT with oral fungal infection and those without infection.

Table 3.13. Comparison of QoL between non-CCRT HNC patients with vs. without oral fungal using the QLQ-HN43

Variables	No CCRT + fungal infection (n = 45)		No CCRT + no fungal infection (n = 54)		p*
	Mean ± SD	Median	Mean ± SD	Median	
Multi-item scales					
Dry mouth/thick saliva	10,00 ± 13,48	0	12,65 ± 19,68	0	0,921
Oral pain	5,56 ± 9,89	0	9,26 ± 14,36	0	0,238
Sensory problems	8,15 ± 17,63	0	8,64 ± 19,89	0	1,000
Social eating difficulties	8,15 ± 14,60	0	9,75 ± 16,48	0	0,588
Swallowing difficulties	7,01 ± 12,95	0	12,81 ± 21,15	0	0,107
Sexuality concerns	14,44 ± 22,64	0	12,35 ± 22,71	0	0,464
Body image concerns	10,00 ± 14,39	0	16,98 ± 22,78	0	0,178
Speech problems	9,93 ± 16,06	0	13,46 ± 19,92	6,67	0,415
Dental problems	5,68 ± 11,02	0	8,23 ± 13,51	0	0,423
Anxiety	17,78 ± 25,72	0	26,54 ± 27,76	33,33	0,071
Shoulder problems	6,29 ± 13,43	0	6,48 ± 17,26	0	0,568
Skin problems	5,93 ± 11,51	0	8,23 ± 18,96	0	0,930
Single-item scales					
Coughing	10,37 ± 17,15	0	12,96 ± 20,90	0	0,611
Impaired mouth opening	6,67 ± 15,24	0	12,96 ± 21,88	0	0,113
Social contact difficulties	6,67 ± 16,82	0	12,96 ± 25,42	0	0,195
Neurological problems	5,18 ± 12,22	0	6,79 ± 13,55	0	0,538
Neck swelling	8,89 ± 20,60	0	10,49 ± 23,19	0	0,775
Concern about weight loss	7,58 ± 18,83	0	14,20 ± 22,06	0	0,062
Delayed wound healing	6,67 ± 15,24	0	12,35 ± 23,61	0	0,275

* *Mann–Whitney test*

There were no statistically significant differences across any QoL domains

between HNC patients without chemoradiotherapy who had oral fungal infection and those without infection.

Table 3.14. Comparison of QoL in HNC patients with oral fungal infection undergoing CCRT vs. No CCRT (QLQ-HN43)

Variables	CCRT + fungal infection (n = 37)		No CCRT + fungal infection (n = 45)		p*
	Mean ± SD	Median	Mean ± SD	Median	
Multi-item scales					
Dry mouth/thick saliva	40,09 ± 22,72	33,33	10,00 ± 13,48	0	< 0,001
Oral pain	19,37 ± 21,88	16,67	5,56 ± 9,89	0	0,001
Sensory problems	31,08 ± 29,70	16,67	8,15 ± 17,63	0	< 0,001
Social eating difficulties	27,25 ± 19,01	16,67	8,15 ± 14,60	0	< 0,001
Swallowing difficulties	27,93 ± 20,53	33,33	7,01 ± 12,95	0	< 0,001
Sexuality concerns	19,37 ± 27,64	0	14,44 ± 22,64	0	0,526
Body image concerns	19,82 ± 24,48	16,67	10,00 ± 14,39	0	0,049
Speech problems	22,34 ± 25,49	13,33	9,93 ± 16,06	0	0,032
Dental problems	14,41 ± 19,04	11,11	5,68 ± 11,02	0	0,017
Anxiety	38,74 ± 27,51	33,33	17,78 ± 25,72	0	< 0,001
Shoulder problems	14,41 ± 19,71	0	6,29 ± 13,43	0	0,057
Skin problems	21,02 ± 18,10	22,22	5,93 ± 11,51	0	< 0,001
Single-item scales					
Coughing	17,12 ± 23,07	0	10,37 ± 17,15	0	0,163
Impaired mouth opening	12,61 ± 21,30	0	6,67 ± 15,24	0	0,179
Social contact difficulties	14,41 ± 24,27	0	6,67 ± 16,82	0	0,108
Neurological problems	16,22 ± 24,37	0	5,19 ± 12,22	0	0,025
Neck swelling	22,52 ± 24,91	33,33	8,89 ± 20,60	0	0,002
Concern about weight loss	35,14 ± 33,28	33,33	7,58 ± 18,83	0	< 0,001
Delayed wound healing	25,23 ± 29,82	0	6,67 ± 15,24	0	< 0,001

* *Mann–Whitney test*

Across the multi-item scales, 10 of 12 domains showed significantly higher symptom scores in patients with oral fungal infection who had undergone CCRT compared with those without CCRT ($p < 0.05$). Similarly, 4 of 7 single-item domains were significantly worse in the CCRT group ($p < 0.05$).

Table 3.15. Comparison of QoL in HNC patients without oral fungal infection undergoing CCRT vs. No CCRT (QLQ-HN43)

Variables	CCRT + no fungal infection (n = 20)		No CCRT + no fungal infection (n = 54)		p*
	Mean ± SD	Median	Mean ± SD	Median	
Multi-item scales					
Dry mouth/thick saliva	37.50 ± 24.71	33.33	12.65 ± 19.68	0	<0.001
Oral pain	16.25 ± 15.64	16.67	9.26 ± 14.36	0	0.028
Sensory problems	25.83 ± 30.81	16.67	8.64 ± 19.89	0	0.001
Social eating difficulties	25.00 ± 22.46	25.00	9.75 ± 16.48	0	0.002
Swallowing difficulties	30.42 ± 26.53	25.00	12.81 ± 21.15	0	0.002
Sexuality concerns	29.17 ± 34.99	16.67	12.35 ± 22.71	0	0.017
Body image concerns	18.33 ± 20.87	16.67	16.97 ± 22.78	0	0.630
Speech problems	20.33 ± 22.11	16.67	13.46 ± 19.92	6.67	0.122
Dental problems	17.78 ± 20.20	11.11	8.23 ± 13.51	0	0.058

Anxiety	37.50 ± 31.93	33.33	26.54 ± 27.76	33.33	0.165
Shoulder problems	17.50 ± 17.50	16.67	6.48 ± 17.26	0	0.001
Skin problems	18.89 ± 20.42	11.11	8.23 ± 18.96	0	0.002
Single-item scales					
Coughing	26.67 ± 33.51	16.67	12.96 ± 20.90	0	0.099
Impaired mouth opening	25.00 ± 30.35	0	12.96 ± 21.88	0	0.121
Social contact difficulties	23.33 ± 26.71	16.67	12.96 ± 25.42	0	0.057
Neurological problems	18.33 ± 22.88	0	6.79 ± 13.55	0	0.023
Neck swelling	20.00 ± 25.13	0	10.49 ± 23.19	0	0.055
Concern about weight loss	25.00 ± 28.36	33.33	14.20 ± 22.06	0	0.096
Delayed wound healing	23.33 ± 26.71	33.33	12.35 ± 23.61	0	0.034

* *Mann–Whitney test*

Significantly higher symptom scores were observed in 10 of 19 QoL domains among patients without oral fungal infection who had undergone CCRT compared with those who had not ($p < 0.05$).

Chapter 4 DISCUSSION

4.1. General Characteristics of the Study Population

In this study, patients with HNC had a mean age of 55.96 ± 11.72 years, with the majority belonging to the 41–60 age group, and a marked male predominance (nearly 86%), consistent with epidemiological trends reported both nationally and internationally. Most patients were of Kinh ethnicity (96.79%) and were commonly engaged in farming, self-employment, or were retired civil servants, with the majority having attained at least a high school level of education. Cervical lymph node metastasis was present in 70.51% of patients at the time of diagnosis, reflecting a high proportion of advanced-stage disease; nasopharyngeal and hypopharyngeal cancers were the most frequent primary sites. Stage IVa accounted for the largest proportion (44.23%), while some patients with early-stage disease were still indicated for CCRT to achieve organ and function preservation, particularly of voice function. Common risk factors and comorbid conditions included a history of tobacco use (47.4%) and mild-to-moderate comorbidities (type 2 diabetes mellitus and cardiovascular or respiratory diseases), whereas the Karnofsky performance status and comorbidity burden were identified as important prognostic indicators. Regarding oral health, most patients reported daily tooth brushing; however, the proportion undergoing regular dental scaling remained low (39.7%), and 15.4% used dental prostheses. These factors may influence the oral microbiota and increase the risk of treatment-related complications during CCRT, underscoring the importance of comprehensive dental assessment and intervention prior to treatment.

4.2. Oral fungal infection, species distribution, and associated factors in patients with HNC

In the present study, the prevalence of oral fungal colonization among HNC patients was 52.26%, whereas oral fungal infection was observed in 48.08% of cases. The colonization rate in our investigation is similar to that reported in Chiang Mai, Thailand (52.26% vs. 53.5%), but lower than those documented in Bangkok (87.5%), Chennai, India (89%), Gujarat, India (70%), Melbourne, Australia (69.2%), San Antonio, USA (73%), and Mainz, Germany (83%). To date, no domestic data on oral fungal colonization rates in HNC patients have been published. In studies of mixed cancer populations, Mai Anh Loi et al. (2017) and Ton Nu Phuong Anh et al.

(2023) reported lower colonization prevalences (43.07% and 45.8%, respectively) than those observed here. This discrepancy may reflect differences in study populations, as oral fungal colonization is less frequent among patients who have not undergone chemotherapy and/or radiotherapy compared to those currently receiving or having completed such therapies.

Of the 82 patients with oral fungal colonization, 75 (91.5%) developed overt fungal infection. Analysis revealed that the infection rate was lowest before CCRT (45.45%), increased to 55.0% after the first dose (20–30 Gy), peaked during the initial treatment course (65.0%), and remained high immediately following completion of therapy (64.71%). The severity of oral mucositis also escalated in parallel with treatment. These findings align with previously published studies and are attributed to an imbalance between fungal virulence factors and host immune defenses induced by CCRT.

In this study, *C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. parapsilosis* accounted for more than 80% of the isolated strains. Among these, *C. albicans* was the most prevalent species, representing over 60% of cases with fungal presence, followed by *C. tropicalis*. These findings are consistent with those reported in previous studies. Notably, a relatively high proportion (>35%) of patients with HNC were infected with non-*albicans* *Candida* species. These species generally exhibit lower susceptibility to antifungal agents compared with *C. albicans*, thereby complicating treatment. In addition, several rare fungal species were documented for the first time in Vietnam, including *C. quercitrusa*, *D. nepalensis*, *C. ethanolica*, and *C. intermedia*. These findings contribute to expanding and refining epidemiological data and enhancing understanding of the microbial ecology of pathogenic agents in Vietnam. Therefore, accurate species identification and antifungal susceptibility testing are essential to optimize treatment outcomes and potentially prevent the emergence of antifungal resistance in patients with advanced-stage cancer.

Various studies have reported conflicting findings regarding the association between oral fungal colonization and factors such as gender, age, education level, occupation, smoking, antibiotic use (within the past month), diabetes mellitus, oral hygiene, denture wearer, cancer stage, and cancer type. In our study, no significant associations were observed between oral fungal carriage and gender, age, diabetes mellitus, denture wearer, cancer stage, or cancer type in patients with HNC. Similar findings were reported in studies conducted in Japan. In contrast, studies from Brazil and Thailand found a higher prevalence of oral fungal colonization in female patients compared to males, and in individuals over 60 years of age compared to those under 60. Likewise, inconsistent results have been reported regarding the relationship between smoking status, antibiotic use, and oral hygiene practices with the occurrence of fungi in oral cavity.

In the current study, univariate analysis identified both weight loss and CCRT as factors associated with oral fungal colonization in patients with HNC. However, in multivariate analysis, only CCRT remained significantly associated with oral candidal carriage. These findings are consistent with previous studies, which have shown that chemoradiotherapy contributes to the onset of both oral mucositis and fungal colonization in this patient population. The underlying mechanisms are thought to involve systemic and local immunosuppression, disruption of oral mucosal integrity, and reduced salivary flow caused by CCRT. Oral fungal infections can make mouth and throat ulcers worse, causing difficulty swallowing, poor nutrition, and weight loss. Therefore, implementing preventive strategies for OC may help reduce oropharyngeal symptoms and improve patients' QoL during cancer treatment.

4.3. Impact of oral fungal infection on QoL in HNC patients undergoing CCRT

4.3.1. Karnofsky performance status

In this study, the majority of patients with HNC had a KPS score ≥ 80 (96.15%), indicating a relatively good baseline functional status prior to treatment, with 83.84% of patients who had not yet undergone chemoradiotherapy achieving a KPS score above 90. However, CCRT resulted in a marked decline in performance status, as evidenced by a statistically significant reduction in KPS scores in the treated group compared with the untreated group ($p < 0.001$), with the proportion of patients with KPS < 80 increasing to 52.63%. This decline reflects the systemic impact and cumulative toxicity of treatment, commonly associated with mucositis, fatigue, swallowing dysfunction, and malnutrition. These findings are consistent with previous studies demonstrating that KPS scores decrease substantially during intensive treatment, reach their lowest levels at the completion of therapy, and subsequently show gradual recovery over the following months, although not fully returning to baseline levels in the short term. In contrast, analysis based on oral fungal infection status revealed no statistically significant difference in the distribution of KPS scores between infected and non-infected patients ($p = 0.096$), suggesting that chemoradiotherapy is the primary determinant of performance status deterioration, although severe oral fungal infection may transiently contribute to KPS reduction through its effects on pain, swallowing ability, and nutritional status.

4.3.2. QoL Assessed by the QLQ-C30 Scale

Before treatment, the mean overall QoL score of patients with HNC in this study was 62.61 ± 20.11 . This score was lower than that reported for the general population in several previous studies, with corresponding mean scores of 66.1 ± 21.7 among 15,386 individuals across 13 European countries, Canada, and the United States; 68.2 ± 20.1 in France; and 77.4 ± 19.8 in the Netherlands. These findings indicate that patients with HNC had already experienced a deterioration in QoL prior to the initiation of treatment, reflecting the burden of disease and cancer-related symptoms, as well as underlying health conditions.

CCRT has been shown to exert adverse short-term effects on patients' QoL. During the course of chemoradiotherapy, this study observed statistically significant differences in QLQ-C30 scores between patients who received CCRT and those who had not yet undergone radiotherapy in the domains of physical, role, and emotional functioning, as well as in symptom scales including fatigue, nausea and vomiting, pain, insomnia, and appetite loss ($p < 0.05$). A prospective study of 63 patients with HNC demonstrated a marked decline in role functioning after approximately four weeks of treatment, which remained at a low level until the end of the 8-week treatment course, reflecting substantial limitations in work capacity and daily activities. Nevertheless, the overall QLQ-C30 global health status/QoL score of patients with HNC generally remained relatively stable throughout the CCRT period, a finding that has also been reported in several other studies.

After completion of CCRT, the QoL of patients with HNC generally tends to improve gradually in parallel with the resolution of acute treatment-related adverse effects. Numerous studies have demonstrated that QLQ-C30 scores may recover within approximately 6–12 months after treatment. In a randomized trial by Curran D. et al., QoL was assessed at baseline, during the fourth week of treatment, and at 4, 8, and 12 months post-treatment; the results showed that QLQ-C30 scores returned to baseline levels after about one year. When analyzed by disease stage, the present study found that only the symptom of nausea and vomiting showed a statistically significant difference between patients with pre-stage III disease and those with stage IV disease ($p = 0.012$). Similarly, several other studies have reported few statistically significant differences in pre-treatment QLQ-C30 scores between early-stage (I–II) and advanced-stage (III–IV) disease. Nevertheless,

disease stage continues to influence QoL trajectories during and after treatment, with patients with advanced-stage disease typically experiencing earlier or more pronounced declines in QoL during the intensive treatment phase

When stratified by performance status and related clinical factors, our study demonstrated statistically significant differences in QoL scores across all four domains of the QLQ-C30 (global health status, functioning, symptoms, and financial difficulties) between patients with a KPS ≤ 80 and those with KPS > 80 . These findings are consistent with the study by Kyrgidis et al., in which a 10% decrease in KPS was associated with a minimum reduction of 8.75 points in global QoL, whereas a 10% increase in KPS corresponded to a minimum increase of 6.63 points. With regard to oral fungal infection status, no statistically significant differences were observed in global health status, functional domains, or symptom scales between patients with and without oral fungal infection, except for the financial difficulties domain ($p = 0.035$). This result is in line with the study by Ferreira et al., which reported no difference in overall QLQ-C30 scores between treatment groups despite varying degrees of oral mucositis. Nevertheless, in our study, CCRT remained a prominent determinant of QoL regardless of oral fungal infection status, with greater functional impairment and increased symptom burden observed in patients who received chemoradiotherapy compared with those who had not yet undergone treatment ($p < 0.05$).

4.3.3. QoL Assessed by the QLQ-HN43 Scale

In Vietnam, several previous studies have evaluated the QoL of patients with various types of HNC. For example, the study by Nguyen Thi Khanh Ha et al. (2016) assessed the QoL of patients with oral cavity cancer prior to treatment at the Ho Chi Minh City Oncology Hospital in 2013; the study by Bui The Anh (2019) investigated the QoL of patients with laryngeal cancer before and after surgery at the National Hospital of Otorhinolaryngology; and the study by Tran Hung (2024) evaluated QoL in patients with nasopharyngeal carcinoma at the National Cancer Hospital (K Hospital). A common feature of these studies is the use of the EORTC QLQ-C30 and EORTC QLQ-HN35 instruments to assess QoL.

The EORTC QLQ-HN35 scale was developed and published in 1999 and has been widely used in studies of HNC. However, since 2014, the European Organisation for Research and Treatment of Cancer (EORTC) has introduced the QLQ-HN43, an updated and expanded version of the QLQ-HN35, with the aim of improving the assessment of QoL in patients with HNC. Nevertheless, in Vietnam, there are currently very few studies that have employed the QLQ-HN43 to evaluate QoL in this patient population. The present study may therefore be among the first conducted in the country to apply the QLQ-HN43 instrument for the assessment of QoL in patients with HNC.

In current study, the analytical results indicated that oral fungal infection did not have a significant impact on overall performance status or on the QoL of patients with HNC. In contrast, the mean scores across most QoL domains were significantly higher in patients who had undergone CCRT than in those who had not yet received radiotherapy. In other words, QoL was markedly impaired following CCRT. Among these domains, the most severely affected were xerostomia/thick saliva (39.18 ± 23.25) and anxiety (38.30 ± 27.08), reflecting a substantial deterioration in QoL related to these problems. Similarly, the study by Leão et al. (2022), which also employed the QLQ-HN43 to assess QoL in patients with HNC after CCRT, reported significant increases in QoL scores in domains such as dysphagia, xerostomia, and thick saliva following treatment, whereas scores related to body image did not change significantly. The findings of Leão et al. are consistent with those of the present study with respect to these domains.

In Vietnam, the study conducted by Tran Hung (2024) addressed the evaluation

of chemoradiotherapy outcomes and QoL in patients with nasopharyngeal carcinoma. However, this study did not specifically analyze the impact of chemoradiotherapy on individual aspects of QoL. Given the limited number of domestic studies on QoL in patients with HNC, the synthesis and comparison of existing findings remain challenging. This situation underscores the need for further in-depth studies to better elucidate the relationship between different treatment modalities and patients' QoL.

The results also showed that QoL scores in most domains tended to increase progressively (reflecting a deterioration in QoL) in a statistically significant manner, with the highest scores observed in patients with HNC who had undergone CCRT and had concomitant oral fungal infection, followed by those who received CCRT without oral fungal infection, and the lowest scores in patients who had not yet undergone radiotherapy. This indicates that patients who received CCRT and simultaneously developed oral fungal infection experienced the poorest QoL. In other words, the combination of CCRT and oral fungal infection appears to have a synergistic effect, exacerbating the decline in QoL in patients with HNC. Previous studies have also provided evidence that both CCRT and oral fungal infection negatively affect oral health and patients' QoL. This is attributable to chemoradiotherapy-induced damage to the oral mucosa, leading to pain and dysphagia; when oral fungal infection occurs concomitantly, these symptoms become more severe. Therefore, the prevention and effective management of chemoradiotherapy-related oral mucosal injury, as well as oral fungal infection, are essential to improve the QoL of patients with HNC during and after treatment.

CONCLUSION

1. Prevalence, species composition, and factors associated with oral fungal infection

- The prevalence of oral fungal colonization was 52.56% (82/156). Among affected patients, 73 (89.02%) were colonized by a single fungal species, while 9 (10.98%) had mixed colonization with 2–4 species. The prevalence was higher in patients receiving CCRT (64.91%) compared with those not yet treated (45.45%).

- A total of 16 fungal species were identified. *C. albicans* accounted for the highest proportion (62.77%), while non-*albicans Candida* species represented 37.23%. Notably, four species - *C. quercitrusa*, *C. ethanolica*, *C. intermedia*, and *D. nepalensis* - were isolated for the first time in patients in Vietnam. Twenty ITS1–5.8S–ITS2 sequences from these 16 species were deposited in GenBank and assigned accession numbers.

- In this study, CCRT was the only factor independently associated with increased risk of oral fungal colonization, raising the risk by 2.07-fold.

2. Impact of oral fungal infection on QoL in HNC patients undergoing CCRT

Impact on QLQ-C30 Scores:

- Patients with oral fungal infection had significantly lower QoL scores in the financial domain compared with those without infection ($p = 0.035$).

- Among patients not yet treated with chemoradiotherapy, those with oral fungal infection had lower constipation and diarrhea symptom scores than those without infection ($p < 0.05$).

- Among patients with oral fungal infection, those who had undergone chemoradiotherapy reported lower QoL in 3 of 5 functional domains (physical, role, emotional) and higher scores in 5 of 8 symptom domains (fatigue, nausea/vomiting,

pain, appetite loss, diarrhea) compared with untreated patients ($p < 0.05$).

- Among patients without oral fungal infection, those who had undergone chemoradiotherapy reported lower QoL in 2 of 5 functional domains (physical and emotional) and higher scores in 4 of 8 symptom domains (fatigue, nausea/vomiting, pain, appetite loss) compared with untreated patients ($p < 0.05$).

Impact on QLQ-HN43 Scores

- Oral fungal infection significantly impaired mouth opening in HNC patients ($p < 0.05$).

- Among patients with oral fungal infection, those who had undergone chemoradiotherapy had significantly higher symptom scores in 14 of 19 domains compared with untreated patients ($p < 0.05$).

- Among patients without oral fungal infection, those who had undergone chemoradiotherapy had significantly higher QoL scores in 10 of 19 domains compared with untreated patients ($p < 0.05$).

- Overall, oral fungal infection exacerbated the decline in QoL among patients receiving CCRT.

RECOMMENDATIONS

- During CCRT, routine screening for early detection of oral fungal colonization should be implemented. In parallel, patient education on proper oral hygiene and oral care should be strengthened to reduce the risk of infection.

- Regular assessment of performance status and QoL using the combined QLQ-C30 and QLQ-HN43 scales is recommended to provide a comprehensive evaluation of patient health, support monitoring of disease progression, and guide appropriate treatment adjustments.

- Further longitudinal studies are needed to evaluate the effectiveness of preventive strategies for OC, measures to reduce mucosal injury, the impact of proactive nutritional interventions, and microbiological–clinical changes in the oral cavity of HNC patients during and after CCRT.

LIST OF PUBLICATIONS RELATED TO THE THESIS

1. Trần Đình Thiết, Nguyễn Văn Ba, Đỗ Thanh Hòa, Đỗ Ngọc Ánh (2025). Ảnh hưởng của hóa xạ trị đồng thời có điều biến liều và nhiễm nấm khoang miệng tới chất lượng cuộc sống bệnh nhân ung thư đầu cổ sử dụng thang đo QLQ-HN43. *Tạp chí Y Dược học Quân sự*, 50(8): 172-180.
2. Tran Dinh Thiet, Vu Anh Hai, Nguyen Van Ba, Dang Duy Cuong, Hoang Dao Chinh, Pham Dinh Khanh, Nguyen Thi Nhu Quynh, Do Ngoc Anh (2025). Prevalence of oral fungal colonization and associated factors in patients with head and neck cancer: A cross-sectional study at four tertiary hospitals in Hanoi, Vietnam. *Tạp chí Y học dự phòng*, 35(5): trang.