

MEDICUS

ISSN 1409-6366 UDC 61 Vol · 30 (3) · 2025

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Betimi i Hipokratit

Në çastin kur po hy në radhët e anëtarëve të profesionit mjekësor premtoj solemnisht se jetën time do ta vë në shërbim të humanitetit. Ndaj mësuesve do ta ruaj mirënjohjen dhe respektin e duhur.

Profesionin tim do ta ushtroj me ndërgjegje e me dinjitet. Shëndeti i pacientit tim do të jetë brenga ime më e madhe. Do t'i respektoj e do t'i ruaj fshehtësitë e atij që do të më rrëfëhet. Do ta ruaj me të gjitha forcat e mia nderin e traditës fisnike të profesionit të mjekësisë.

Kolegët e mi do t'i konsideroj si vëllezër të mi.

Në ushtrimin e profesionit ndaj të sëmurit tek unë nuk do të ndikojë përkatësia e besimit, e nacionalitetit, e racës, e politikës, apo përkatësia klasore. Që nga fillimi do ta ruaj jetën e njeriut në mënyrë absolute. As në kushtet e kërcënimit nuk do të lejoj të keqpërdoren njohuritë e mia mjekësore që do të ishin në kundërshtim me ligjet e humanitetit. Këtë premtim po e jap në mënyrë solemne e të lirë, duke u mbështetur në nderin tim personal.

The Oath of Hippocrates

Upon having conferred on me the high calling of physician and entering medical practice, I do solemnly pledge myself to consecrate my life to the service of humanity. I will give my teachers the respect and gratitude which is their due. I will practice my profession with conscience and dignity. The health of my patient will be my first consideration. I will respect the secrets which are confided in me, even after the patient has died. I will maintain by all the means in my power, the honor and the noble traditions of the medical profession.

My colleagues will be my brothers.

I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient. I will maintain the utmost respect for human life from its beginning even under threat and I will not use my medical knowledge contrary to the laws of humanity. I make these promises solemnly, freely and upon my honor

Medical Journal

MEDICUS

ISSN 1409-6366 UDC 61 Vol · 30 (3) · 2025

Revistë Shkencore Nderkombëtare e Shoqatës së Mjekëve Shqiptarë të Maqedonisë
International Journal of Medical Sciences of the Association of the Albanian Doctors from Macedonia

Botues/ Publisher: **SHMSHM / AAMD**

Tel. i Kryeredaktorit / Contact: **+389 (0) 71 240 927**

Zhiro llogaria / drawing account: **200-000031528193**

Numri tatimor / tax number: **4028999123208**

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Design & Layout

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Printed in:

Print House “Pruf Print”, Skopje
The Journal Medicus is printed and distributed free
of charge with a circulation of 600 copies.

EVALUATION OF THE CLINICAL AND HISTOPATHOLOGICAL CHARACTERISTICS OF THE TUMOR AS FACTORS FOR THE OCCURRENCE OF METASTASES IN THE CERVICAL LYMPH NODES IN SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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Medicus 2025, Vol. 30 (3): 385-391

ABSTRACT

Introduction: Squamous cell carcinomas in the maxillofacial region exhibit a significant predisposition for metastasizing to the cervical lymph nodes, which constitutes a negative prognostic factor. In clinical practice, the TNM classification is employed for treatment planning; however, it does not provide insights into the histological characteristics of the tumor, which offer predictive information for subsequent treatment and prognosis.

Patients and methods: This study was conducted on 74 patients who underwent surgery in the Department of Maxillofacial Surgery at the Clinical Hospital in Stip, during the period from February 2022 to March 2024. All patients underwent resection of the primary tumor and appropriate neck dissection. The clinical assessment included the location and size of the tumor, as well as nodal status. The histological evaluation encompassed depth of invasion, degree of differentiation, lymphovascular and perineural invasion, and the stage of the disease.

Objective: The aim of this study is to present an evaluation of the clinical and histopathological features of the tumor as factors influencing the occurrence of metastases in the cervical lymph nodes in cases of squamous cell carcinoma of the head and neck.

Results: We identified a correlation between the clinical nodal stage and the assessed histopathological characteristics of the tumor. Depth of invasion, poor pathological differentiation, and lymphovascular invasion were considered risk factors for the development of cervical lymph node metastases and an unfavorable prognosis.

Conclusion: The evaluation of the histopathological features of the tumor should be the initial step in investigating their role as significant predictors of the occurrence of neck metastases. The findings of this study may contribute to the establishment of criteria for assessing the risk of metastasis and the prognosis of patients with HNSCC.

Keywords: cervical lymph nodes, prognostic factors, elective neck dissection, HNSCC

INTRODUCTION

Squamous cell carcinoma of the head and neck represents the most prevalent and aggressive form of malignancy, characterized by a dismal prognosis and a significant propensity for metastasis (1). Its treatment encompasses radical surgical excision and elective neck dissection,

succeeded by radiotherapy targeting the clinically positive neck (2). Patients diagnosed with squamous cell carcinoma at an early stage typically exhibit a favorable prognosis, whereas those presenting with evident cervical lymph node or distant metastases face a grim outlook. Cervical lymph node metastases diminish the

five-year survival rate to below 50%, thus rendering the management of cervical metastases a critical factor in enhancing survival rates for these patients (3). The most pivotal prognostic factor influencing the behavior and outcome of the tumor in SCC is the presence and extent of involvement of the cervical lymph nodes. Their diagnosis is established through radiological procedures (ultrasonography, CT, MRI) and fine needle aspiration biopsy (FNAB).

Squamous cell carcinoma primarily disseminates through the lymphatic vessels. The lack of fascial sheaths between the internal and external muscles facilitates the tumor's penetration into the muscles and surrounding structures. Numerous clinical and histopathological characteristics serve as predictors for the occurrence of neck metastases.

Tumor location - While the site of the tumor has been considered a determinant in several prior studies, there remains no definitive consensus regarding which localization poses a greater risk for metastasis. Typically, squamous cell carcinoma in the oral cavity exhibits a higher incidence of metastasis.

Tumor size - According to the TNM classification, tumor size is defined as the largest surface dimension, specifically the diameter of the tumor. Numerous studies have elucidated a correlation between tumor size and an elevated risk of neck metastases (4). T1 tumors have been documented to exhibit fewer metastases compared to advanced T3 and T4 tumors (5).

Depth of invasion - Depth of invasion is quantified by the vertical measurement from the skin surface (mucosa) to the maximum point of invasion (6). This factor is regarded as a more precise histological predictor of nodal metastases, local recurrence, and survival than tumor size. Bier-Laning et al. 2009, found that every 1 mm increase in depth of invasion elevates the probability of metastasis by approximately 5% (7).

Tumor differentiation—The histological grading of tumors according to Broder's classification—is divided into three categories: grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated). The subjective assessment of the degree of keratinization, cellular and nuclear pleomorphism, and mitotic activity is taken into account (8). Nevertheless, an increasing number of authors highlight the poor correlation between histological grading and both prognosis and response to treatment. Nonetheless, the

results of several prior studies suggest that histological grading serves as a significant and independent predictor of the occurrence of metastases in cervical lymph nodes in head and neck squamous cell carcinoma (9).

Lymphovascular invasion - Lymphovascular invasion, as part of the multifactorial grading system proposed by Jakobson, is classified according to the presence or absence of tumor cells located in the walls or lumens of blood and lymphatic vessels (10). Lymphovascular invasion has a significant relationship with the localization, size, and thickness of the tumor, histological grading, as well as metastasis in the cervical lymph nodes, local recurrence, and survival (11). Muscle infiltration is a factor that can be measured objectively. It delineates the presence of tumor cells in the immediate vicinity of the superficial or deep muscle tissue. It has been demonstrated to be a reliable and adequate predictive factor for metastasis to the lymph nodes (12). Byers et al. propose that the likelihood of occult metastases escalates if muscle invasion surpasses 4 mm (13).

The treatment of clinically negative cervical lymph nodes (N0) represents a significant challenge for maxillofacial surgeons, since there are no reliable parameters for predicting occult metastases. To assess their existence, some histopathological tumor characteristics, such as depth of invasion, degree of differentiation, lymphovascular and perineural invasion.

Recently, in its eighth edition, the American Joint Committee on Cancer/The Union for International Cancer Control (UICC) describes the depth of invasion (DOI) as a predictor of the occurrence of cervical lymph node metastases (14,15), and proposes the category T in the TNM classification for the depth of invasion (DOI) of the primary tumor. According to the pathohistological finding, the degree of tumor invasion is classified as thin T1 (<5 mm), intermediate T2 (5-10 mm) and thick T3, T4 (> 10 mm) (16).

In addition to the depth of invasion, predictive risk factors encompass tumor budding (TB), the pattern of invasion (POI), lymphovascular invasion (LVI), and perineural invasion (PNI), as well as the tumor-stromal ratio (TSR), which reflects the degree of differentiation (17, 18, 19). Depth of invasion (DOI) and tumor thickness—are these two distinct factors sufficient to provide prognostic information?

Although both factors signify invasion in depth, they are evaluated through different methodologies. Depth

of invasion (DOI) is determined by drawing a line from the basement membrane of the adjacent intact skin or mucosa to the deepest point of invasion (20), whereas tumor thickness is measured from the surface of the carcinoma to the deepest point of invasion. The average values for tumor thickness and depth of invasion reported in the literature vary, ranging from 1.5 to 10 mm (21).

Although the impact of Depth of Invasion (DOI) on the clinical staging of tumors, and consequently their prognosis, has demonstrated significant results, longer-term follow-up of prospective studies remains necessary to furnish sufficiently robust evidence regarding its role as a predictor of neck metastases and overall prognosis. In exophytic tumors, tumor thickness exceeds DOI, whereas in endophytic tumors, the converse is true; the thickness is less than DOI. Several studies indicate that depth of invasion (DOI) is a significant predictor of the occurrence of cervical lymph node metastases. Additionally, some studies identify DOI as an independent risk factor for recurrence and survival duration.

A limiting characteristic of the depth of invasion (DOI) is that it is determined through pathohistological evaluation conducted a few days after the surgical resection of the tumor. Unfortunately, there exists no reliable method for its assessment prior to or during surgery. It can only be evaluated from the material obtained through incisional biopsy; however, these results are often unreliable and may yield conflicting outcomes. Although the DOI cutoff values adopted by the American Joint Committee on Cancer (AJCC) are universal for all localizations within the maxillofacial region, various anatomical areas may possess distinct and specific cutoff values to enhance prognostic potential. In order to achieve a clear identification of high-risk predictive factors that contribute to the occurrence of neck metastases, the presence of metastasis is essential.

Five-year survival rates vary according to tumor size, with T1/T2 tumors classified as low-risk and T3/T4 tumors categorized as high-risk (22). The prognosis is also influenced by the location of the primary tumor, lymph node involvement, tumor thickness, and the status of surgical margins. Neck lymph node metastases are observed in approximately 40% of patients diagnosed with oral and maxillofacial squamous cell carcinoma. The detection of neck metastases at the time of initial diagnosis is critical for treatment planning, prognosis, and patient survival. This retrospective study aimed to investigate the role of different clinicopathologic

features of the primary tumor as predictors of nodal neck metastases in patients with T1/T2/T3 head and neck squamous cell carcinoma.

METHODS AND MATERIAL

This study presents a prospective and retrospective analysis of 74 patients with histopathologically confirmed squamous cell carcinoma (SCC). Patients underwent surgical intervention at the Department of Maxillofacial Surgery, Clinical Hospital Stip, during the period from 2022 to 2024, with varying cancer localizations. Individuals with pathohistological findings indicative of cancer types other than squamous cell, those exhibiting distant metastases, and those receiving palliative radiotherapy were excluded from this analysis. Statistical analysis of descriptive parameters was conducted via SPSS 27.0. Fundamental information encompasses gender, age, tumor location, tumor size, histopathological characteristics of the tumor, and nodal status. The patho-histological diagnosis was rendered following the radical removal of the tumor by the pathologists of the Department of Pathology, Clinical Hospital Stip. Informed consent was obtained from all participants in this clinical study. These data are presented in tables, respectively.

RESULTS

Of the 74 patients included in this study, 49 (66.22%) were male and 25 (33.78 %) were female. Only one patient (1.35%) was under 50 years of age, 8 patients (10.81%) were 50-60 years of age, 34 patients (45.95 %) were 60-70 years of age, and 31 patients (41.89 %) were over 70 years of age. The distribution of patients by gender and age is presented in Table 1.

Table 1. Demographic data results

	Patient gender		Age of patients by group	
	male	female	up to 50 years of age	1 (1.35%)
	49 (6.22 %)	25 (33.78 %)	50-60 age	8 (10.81 %)
			60-70 age	34 (45.95 %)
			over 70 years of age	31 (41.89 %)
Total number of patients	74			

In Table 2, we present the results of the evaluation of cancer localization by group. According to the localization in 17 patients (22.97%), the carcinoma is situated on the skin of the face; in 6 patients (8.11%), the localization is on the skin of the neck; in 6 patients (8.11%), the carcinoma is found on the nose; in 21 patients (28.37%), the localization is on the lower lip; in 3 patients (4.06%), it is located in the parotid gland; in 4 patients (5.41%), the carcinoma is found on the auricle; and in 17 patients (22.97%), it is localized in the oral cavity (buccal mucosa and tongue). Most of the tumors are localized on the lower lip and oral mucosa.

Table 2. Cancer localization by group

Cancer localization by group	facial skin cancer – 17 patients (22.97 %)
	lower lip cancer – 21 patients (28.37 %)
	parotid gland cancer – 3 patients (4.06 %)
	neck skin cancer – 6 patients (8.11 %)
	nose cancer – 6 patients (8.11 %)
	ear auricle cancer – 4 patients (5.41 %)
	oral cavity cancer – 17 patients (22.97 %)

In table 3, we present number of patients according to tumor size and clinical nodal status. According to tumor size, in 2 patients (2.70%), the diameter measures up to 1 cm; in 44 patients (59.46 %), it ranges from 1 to 3 cm; and in 28 patients (37.84%), the tumor exceeds 3 cm.

Table 3. Number of patients categorized by tumor size and clinical nodal status

Tumor size	Number of patients
to 1 cm	2 (2.70 %)
1-3 cm	44 (59.46 %)
up to 3 cm	28 (37.84 %)
total patients	74
Clinical neck nodal status	Number of patients
N0	52 (70.2 %)
NI	16 (21.62 %)
NII	6 (8.11 %)
total patients	74

There are 52 (70.27 %) patients with N0 stage, 16 (21.62 %) patients with NI and 6 (8.11%)

patients with NII.

Table 4. Depth of invasion the tumor

Depth of cancer invasion	N-status (number of patients)
It reaches the lamina propria- 8 patients (10.81%) <2mm	N0
Dermal layer of skin- 16 patients (21.62 %) >3mm	N0
Subcutaneous fat – 11 patients (14.87 %) >4mm	NI(1)
Muscle layers – 32 patients (43.25 %) >5mm	NI (14) NII (4)
Surrounding glandular tissue – 3 patients (4.05%)	NI (1) NII (1)
Cartilage- 4 patients (5.40%)	NI (1)

The depth of tumor invasion and its relation with nodal status are depicted in Table 4.

In terms of the depth of invasion, 8 patients (10.81%) exhibited tumors that reached the lamina propria, 16 patients (21.62%) had tumors penetrating into the dermal layer of the skin, 11 patients (14.87%) showed penetration into the subcutaneous fat tissue, 32 patients (43.25%) demonstrated involvement of the muscle layers, 3 patients (4.05%) had involvement of the surrounding glandular tissue, and 4 patients (5.40%) exhibited tumors that penetrated into the cartilage. In eight patients in whom the tumor reached the lamina propria, no neck metastases were identified (N0). In 16 patients with tumor penetration into the dermal layer (>3mm), neck metastases were likewise not diagnosed. In 11 patients with penetration into subcutaneous fat tissue (>4mm), only one exhibited enlarged lymph nodes at the NI level. In 32 patients with infiltration of the muscle layers (>5mm), fourteen presented with NI level involvement, and four had neck metastases at the NII level. In 3 patients with malignant neoplasms of the parotid gland, one presented with involvement at the NI level, while another exhibited metastatic lymph nodes at the NII level. Ultimately, among 4 patients diagnosed with squamous cell carcinoma of the auricle, only one demonstrated metastases at the NI level. Radical excision of the lesion was conducted in all patients. In 22 patients with a radiographic diagnosis of node-positive neck, selective neck dissection was undertaken. Histopathological findings corroborated the

presence of metastatic changes in the lymph nodes.

Table 5. The degree of tumor differentiation and nodal status

Degree of differentiation – total number 74	Nodal status/ %
Well-differentiated carcinoma (G1)- 42 patients (56.76%)	N0
Moderately differentiated carcinoma (G2)- 27 patients (36.48%)	NI - 17 patients (22.97%)
Poorly differentiated carcinoma (G3)- 5 patients (6.76%)	NII- 5 patients (6.76%)

The evaluation of tumor differentiation and its relationship to neck metastases is presented in Table 5. According to the degree of tumor differentiation, 42 patients (56.76%) were diagnosed with well-differentiated carcinoma (G1), 27 patients (36.48%) with moderately differentiated carcinoma (G2), and 5 patients (6.76%) with poorly differentiated carcinoma (G3).

In a cohort of 42 patients with well-differentiated tumors, no instances of neck metastases were observed. Among 27 patients exhibiting moderate differentiation, 17 were diagnosed with Nodal Metastasis Level NI, while all 5 patients with poor differentiation presented with Nodal Metastasis Level NII.

Table 6. Tumor staging and Lymphovascular / Perineural invasion

Stage	Number of patients
Stage I	49 (66.22 %)
Stage II	19 (25.67 %)
Stage III	4 (5.41 %)
Stage IV	2 (2.70 %)
	total 74
Lymphovascular / Perineural invasion	Number of patients with Lymphovascular / Perineural invasion
Lymphovascular invasion	22 (29.73 %)
Perineural invasion	3 (4.05 %)
	total 25 of 74 (33.78 %)

The number of patients exhibiting lymphovascular and perineural invasion is detailed in Table 6. According to the histological stage of the disease, 49 patients (66.22%)

are classified as stage I, 19 patients (25.67%) as stage II, 4 patients (5.41%) as stage III, and 2 patients (2.70%) as stage IV. Lymphovascular invasion was identified in 22 patients (29.73%), whereas perineural invasion was observed in 3 patients (4.05%). Among the total number of subjects, 43 exhibited an invasion depth exceeding 4mm, of which 22 demonstrated lymphovascular invasion histopathologically. An equivalent number presented with a positive neck nodal status. Perineural invasion was detected in only 3 subjects.

DISCUSSION

This study presents an evaluation of the clinical and histopathological features of the tumor as factors influencing the occurrence of metastases in the cervical lymph nodes in cases of squamous cell carcinoma of the head and neck. In the past, treatment planning and prognosis were based on TNM staging, excluding the biological characteristics of the tumor. Consequently, histopathological features of the tumor serve as a crucial factor for treatment planning, prognosis, and insights into the aggressiveness of the disease.

Previous studies on squamous cell carcinoma have shown that depth of invasion, tumor size, and stage of the disease are important parameters in predicting the occurrence of nodal metastases. Depth of invasion is considered an objective parameter and has been evaluated by several investigators for HNSCC (23).

In our study, among the 74 patients examined, only 5 exhibited poorly differentiated squamous cell carcinoma, while 27 presented with moderately differentiated squamous cell carcinoma and 42 patients were diagnosed with well-differentiated carcinoma. It is noteworthy that only 22 patients were found to have metastases in the cervical lymph nodes, and none of these patients belonged to the group with well-differentiated carcinoma.

Among our patients with a depth of invasion of up to 4 mm (totaling 24), no metastases were detected in the cervical lymph nodes; however, in those with a depth of tumor invasion exceeding 5 mm (totaling 43), cervical nodal metastases were identified in 15 patients at the NI level and in 4 at the NII level.

In patients with malignant neoplasms of the parotid salivary gland, out of a total of three, two exhibited neck metastases, one at the NI level and the other at the NII level. Among four patients diagnosed with squamous cell carcinoma of the auricle featuring cartilage invasion,

only one presented with neck metastases at the NI level.

In order to compare our results with similar findings, we conducted a thorough review of the literature and discovered a retrospective study by Rikardsen et al., which examined 133 patients with squamous cell carcinoma (SCC); of these, 42% were classified as well-differentiated, while 8% were deemed poorly differentiated (24).

In a study by Akhter et al., (25) of 50 patients with oral squamous cell carcinoma, 18% of well-differentiated patients had nodal metastases, 26% of moderately differentiated patients, and all poorly differentiated patients had cervical lymph node metastases.

In a study by Kurokawa et al., (26) of 50 patients with SCC, 3.1% of well-differentiated patients had nodal metastases, and 33.3% of moderately differentiated patients had cervical metastases.

Some studies have compared tumor thickness and DOI (27, 28, 29). In the study by Dirven et al. (27), it was found that only 5.7% of patients had a different T stage when thickness was used instead of depth. However, the overall survival outcome was quite similar when thickness or depth were used as prognostic factors. Liu et al. (28) in their study found that both factors have a significant correlation in the occurrence of metastases in the cervical lymph nodes, and the boundary dimensions for the occurrence of cervical metastases were taken as 4.5 mm for depth and 8 mm for tumor thickness.

According to the results of the International Consortium for Outcome Research, a multi-institutional study conducted on 3149 patients showed that each increase in DOI by 5 mm also increases the T category (T1 <5mm, T2 5-10mm, T3/T4 >10mm) (29).

CONCLUSION

The histopathological characteristics of the tumor serve as a robust predictor of disease progression and metastasis. In instances where the depth of invasion (DOI) exceeds 5mm, elective neck dissection (levels I-III) is mandated. Conversely, in cases where the DOI is less than 5mm, stringent patient monitoring and regular evaluations are essential. Our study concludes that there is a heightened incidence of metastases in the cervical lymph nodes associated with moderately and poorly differentiated squamous cell carcinoma (SCC), as well as in tumors exhibiting a depth of invasion greater than 4mm. Lymphovascular invasion demonstrates a significant

correlation with the occurrence of metastases in the cervical lymph nodes. Therefore, we are able to assess the aggressiveness of the tumor, predict the prognosis, and devise appropriate treatment strategies for the neck. The evaluation of the histopathological features of the tumor should be the initial step in investigating their role as significant predictors of the occurrence of neck metastases. The findings of this study may contribute to the establishment of criteria for assessing the risk of metastasis and the prognosis of patients with HNSCC.

Conflict of Interest: None declared

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