

# Factors Influencing Lymph Node Metastasis From Supraglottic Laryngeal Carcinoma

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**Abstract-** In patients with supraglottic carcinoma (SGLC), lymphatic metastasis is frequent and can cause a significant reduction in local control rate and survival. Currently, the preferred method of neck treatment in patients with supraglottic cancer is prophylactic bilateral neck dissection that could result in overtreatment in at least two thirds of patients. The purpose of this study is to evaluate factors influencing neck metastasis and to determine whether routine elective neck dissection is necessary for the management of all SGLCs. 66 patients with SGLCs who underwent transoral laser surgery and neck dissection were included in this study. The rate of overall and occult lymphatic involvement was 29% and 20%, respectively. The most common involvement site was level II, and factors such as T category, tumor grade, epilarynx involvement, and extension of tumor to the medial wall of pyriform sinus were significantly related to cervical lymph node metastasis. In conclusion, our results suggest that in selected patients with SGLC (such as small T1 or lateralized tumors), elective neck treatment could be ignored, and instead, close follow-up be considered.

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## Introduction

Regional lymphatic status in head and neck malignancies has an important role in local control rate and prognosis, especially in the supraglottic larynx because of the rich and bilateral lymphatic network (1). In patients with supraglottic laryngeal carcinoma (SGLC), cervical lymph nodes involvement cause a significant reduction in local control rate and survival (2). Accurate diagnosis and appropriate treatment planning for cervical lymph nodes are important to balance between complications of unnecessary extensive neck surgery and risk of neck relapse (3). Cervical lymphatic involvement is diagnosed through physical examination and imaging studies (clinically positive neck) or histological evaluation after neck dissection despite negative examination or imaging (occult positive neck) (2). Factors such as T category of tumor according to Tumor Node Metastasis of American Joint Committee of Cancer (AJCC TNM), histopathological grade, and localization of tumor affects the incidence of cervical

metastasis in supraglottic carcinoma (4,5). For instance, the Involvement of the epilarynx, which includes suprahyoid epiglottis, aryepiglottic folds, and arytenoids, has been associated with an increased chance of lymphatic metastasis in some studies (6).

Treatment of patients with head and neck cancer who have a clinically negative cervical lymph node (N0) remains controversial. The routine use of surgery or radiation for all N0 patients would result in the overtreatment of many patients. On the other hand, close observation of patients and therapeutic neck dissection once regional metastases become apparent may delay diagnosis and treatment of the disease and result in a less favorable prognosis (7).

Currently, for most head and neck surgeons, observation is the preferred method when the possibility of occult metastasis is less than 20%, and elective neck treatment is preferred if the probability of metastasis is greater than 20% (8).

The incidence of cervical lymph node metastasis in supraglottic cancer has been reported up to 35% in some

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studies. Therefore, prophylactic bilateral neck dissection has been accepted as part of treatment in all patients except for those with small T1 tumors (6). Elective treatment of the neck in every SGLC patient could result in overtreatment of at least two thirds of patients with a concomitant unnecessary increase in morbidity, hospitalization time, and treatment costs.

Indications of neck dissection in transoral laser microsurgery (TLM) is the same as open surgery, but in most centers, it's done 3-4 weeks after primary surgery, which leads to an increase in cost treatment time and may delay adjuvant treatments.

Obviously, identifying low-risk patients for cervical metastasis could decrease the need for elective treatment and its consequences in patients with SGLC. It is especially more important for laser supraglottic laryngectomy candidates as it will prevent unnecessary hospital admission second operation and will shorten the overall treatment time.

Considering above mentioned reasons, we conducted this study to evaluate the relationship between T category, histopathological grade, and localization of tumors with cervical lymphatic metastasis. The final purpose of this study was to determine whether routine elective neck dissection is necessary for the management of all SGLCs.

## Materials and Methods

The study population was patients with supraglottic Squamous cell carcinoma who were referred to Amiralam hospital, Tehran University of Medical Sciences, during 2015-2018. Patients whose tumors were not completely resectable with TLM (such as cartilage erosion or extralaryngeal extension) and who received any previous therapy such as radiation or open surgery were excluded. The study was approved by the institutional research ethics committee, and patients were informed about the objectives of the study and signed informed consent forms. Demographic, clinical, and pathologic data of patients were collected. The extent of disease and involvement of supraglottic subunits were determined by direct laryngoscopy, computed tomography, and/or magnetic resonance imaging. Patients without evidence of lymphatic involvement on palpation and imaging studies were defined as clinically N0. Imaging features

such as nodal size, nodal shape, or the presence of central necrosis were used to identify patients with metastatic adenopathy, as these are the usual diagnostic criteria in most studies (9,10). Clinical and pathologic staging was recorded according to the 2010 AJCC staging system.

Three to four weeks after TLM patients were scheduled for selective neck dissection (level II-IV) for clinically N0 patients and II-V in clinically N+ patients if lymph node involvement was confirmed by frozen section. During dissection, the boundaries of each level were tagged by silk suture, and after en-block resection of fibrofatty tissue, each level was evaluated individually by histopathological analysis.

After collecting data and histopathological analysis, the rate of overall and occult lymphatic metastasis and the rate of each level involvement were measured. Occult lymphatic metastasis was used in patients who were clinically N0 but had lymphatic involvement in histopathologic analysis. The relationship between variables and overall and occult lymphatic metastasis was evaluated using the *chi*-square test with statistical significance at 0.05 level.

## Results

Sixty-six patients were included in this study (64 male and 2 female patients). Patients' ages ranged between 40 and 75 years, with a mean age of 59 years. Clinical details are summarized in table 1.

Of the 66 patients in the study, 19 patients had a pathologic involvement of the lymph nodes after neck Dissection. Of these patients, 13 patients had no evidence of lymph node involvement in pre-treatment assessments such as clinical examinations, ultrasound, and computed tomography (CT) scans (occult metastasis). Therefore, overall and occult lymphatic involvements are 29% and 20%, respectively.

From the dissected levels, the most common involvement site was the lymphatic of level II (from skull base to hyoid bone), which was involved in 18 patients (94.7%). Single involvement of level III was observed in one patient. However, there was no patient with isolated involvement of level IV in the absence of level II or III involvement (Table 2).

**Table 1. Tumor characteristics in patients with supraglottic cancer**

Variable		Number (%)
T stage	T1	2 (3%)
	T2	30 (45%)
	T3 <sup>±</sup>	34 (52%)
N stage(pathologic)	N0	47(71%)
	N1	13 (20%)
	N2	6 (9%)
Stage	N3	0 (0%)
	I	2 (3%)
	II	23 (35%)
	III	35 (53%)
	IVA	6 (9%)
Grade	Well diff	31 (47%)
	Mod diff	26 (39%)
	Poorly diff	9 (14%)
Epilarynx	Free	24 (36%)
	Involved	42 (64%)
Medial wall of pyriform sinus	Free	50 (76%)
	Involved	16(24%)

**Table 2. Distribution of cervical level involvement in patients with cervical metastasis**

Involved levels	Number (%)
Level II	12 (63.2%)
Level III	1 (5.3%)
Level IV	-
Level II, III	4 (21.1%)
Level II, IV	1 (5.3%)
Level II, III, IV	1 (5.3%)
Total	19 (100%)

The relationship between T category of tumor and rate of occult and overall lymph nodes involvement has been shown in table 3. No lymphatic involvement is seen in T1 patients. The lymphatic involvement rate for T2 patients was 17% (5 of 30 patients), while this rate was 59% and significantly higher in patients with T3 tumor (14 of 34 patients) ( $P=0.00$ ). This relation was also significant in the rate of occult lymphatic involvement (11% in T2 patients compared to 29% in T3 patients) ( $P=0.03$ ).

The relationship between the grade of tumor and overall and occult cervical lymph nodes metastasis was calculated. As seen in table 3, by increasing the degree of differentiation, the chance of cervical metastasis decreases. This relationship is significant for occult and overall cervical metastasis ( $P=0.00$ ).

There was a statistically significant relationship between the involvement of epilarynx and occult ( $P=0.014$ ) and overall cervical lymph node metastasis ( $P=0.000$ ). Among patients with free epilarynx, only 2

patients had cervical metastasis that was N0 in pre-treatment assessments (8%). For patients with involvement of epilarynx, the rate of overall and occult cervical metastasis was 40% and 26%, respectively (Table 3).

The involvement of the medial wall of the pyriform sinus was significantly related to cervical lymph node metastasis ( $P=0.00$ ). There were 16 patients with involvement of medial wall of pyriform sinus, of which 56% had involved neck lymph nodes, and six of them were N0 in pre-treatment assessment.

Because of the bilateral lymphatic drainage pathway of the supraglottis, the likelihood of bilateral or contralateral lymphatic metastases is higher in supraglottic carcinoma. We sought to define the risk of bilateral and contralateral neck metastasis in the studied patients. In this study, midline structures were involved in almost all patients except for two that in none of them cervical metastasis is seen. In patients in whom the tumor

## Cervical metastasis in supraglottic cancers

was limited to infrahyoid epiglottis without aryepiglottic fold or ventricular band involvement (4 cases), no cervical metastasis was found.

In other patients in whom the tumor was more lateralized, or epiglarynx was involved (60 patients), first of all, the epicenter of the tumor was identified by direct vision and imaging studies. Based on these findings, the patients were categorized into two groups: patients with tumors mainly in one side that crossed the midline,

however, with minimal contralateral involvement, and patients with tumors equally involving both sides of supraglottis. In the first group, metastasis was mainly ipsilateral though one patient had only contralateral involvement. In another group, the distribution of unilateral and bilateral metastasis was equal (Table 4). We didn't find a statistically significant difference between groups.

**Table 3. Probability of occult and overall lymph node metastasis in relation to T stage, tumor grade, and site of supraglottic involvement**

Variable	Overall Lymphatic Involvement (number, percent)	Occult Lymphatic Involvement	Statistically significance $P \leq 0.05$
T stage	T1	0 (0%)	Nil
	T2	5 (17%)	+
	T3	14 (59%)	+
Grade	Well diff	2 (6%)	+
	Moderate diff	11 (42%)	+
	Poorly diff	6 (66%)	+
Epilarynx	Free	2 (8%)	+
	Involved	17 (40%)	+
The medial wall of the pyriform sinus	Free	10 (20%)	+
	Involved	9 (56%)	+

**Table 4. Distribution of ipsilateral, contralateral, and bilateral lymph node metastasis in relation to supraglottis site of involvement**

Site of involvement	Number	Lymph node metastasis		
		Ipsilateral	Contralateral	Bilateral
Infrahyoid epiglottis	4	0	0	0
lateral side of supraglottis, no midline involvement	2	0	0	0
the lateral side of the supraglottis crossed the midline	41	7	1	4
Both lateral sides of supraglottis involvement	19	3	0 <sup>±</sup>	4

<sup>±</sup>Ipsilateral or contralateral was defined based on tumor epicenter

## Discussion

Approach to cervical lymph nodes in clinically N0 patients with supraglottic SCC is controversial, and there are questions about the indication and extent of neck

dissection in this group of patients. Prophylactic neck dissection may reduce the rate of regional recurrence but increase the risk of complications, especially in the dissection of level IV (2,11). By restricting neck dissection surgery to N0 patients with a high risk of

lymphatic involvement according to the site, grade, and stage of the tumor, it's possible to avoid complications of neck surgery in a large group of patients. It also allows starting adjuvant therapy earlier and getting patients back to normal life sooner.

In different studies, the rate of occult lymphatic metastasis in supraglottic cancer ranged between 4 to 35% (6). In our study, the rate of occult lymphatic metastasis was 20% which was similar to other studies. According to previous studies, by increasing the T category of the tumor, the incidence of occult metastasis increased (4,5). The incidence of occult lymphatic metastasis in our T2 patients was 11% which was significantly lower than T3 patients (29%). Interestingly we didn't find any cervical metastasis in T1 patients. Due to the low probability of lymphatic involvement in T1 and T2 patients (less than 20%), we could recommend postponing elective neck dissection in these low-risk groups of patients instead of following them closely. However, our data provide limited information about this issue, which needs a larger number of patients to be generalized.

The relationship between the grade of tumor and lymphatic metastasis has been proven in various studies. The less differentiated tumor, the greater risk of lymphatic metastasis (3,4,12). In our study, similar to other reports, there was a relationship between grade of tumor and lymphatic involvement, which was statistically significant for occult and overall lymphatic metastasis.

There are different approaches for the localization of primary tumors. In 2007, Yüce *et al.*, divided T1 and T2 supraglottic SCCs into two groups based on the involvement of the epilarynx. Epilarynx contains marginal structures: suprahyoid epiglottis, aryepiglottic folds, and arytenoids. They found a significant relationship between the involvement of the epilarynx and occult cervical metastasis (6). In our study, occult lymphatic involvement in patients with involvement of epilarynx was 26% which was significantly higher than 8% in patients with free epilarynx. This relationship was also seen between overall lymphatic metastasis and involvement of the epilarynx.

Other studies investigated the location of the tumor (central or lateralized) and ipsilateral and contralateral lymphatic involvement. According to these studies, the risk of contralateral lymphatic metastasis in clearly lateral lesions which not cross the midline was lower than 10%. The risk of bilateral lymphatic metastasis increased with the involvement of central structures. Therefore, these studies suggested ipsilateral elective neck dissection for N0 patients with clearly lateral lesions. They considered

bilateral neck dissection for central or bilateral tumors and lateral tumors with clinical involvement of ipsilateral lymph nodes (5,13). In our study, midline structures such as epiglottis and preepiglottic space were involved in almost all patients, so we could not investigate contralateral lymphatic involvement in clear lateral lesions. Contralateral lymphatic involvement was seen in patients whose cancers largely involved one side and crossed midline structures. Contralateral lymph nodes metastasis without the involvement of ipsilateral lymph nodes was seen in only one patient; however, in bilateral lesions, bilateral lymphatic involvement was seen frequently. We cannot obtain a reliable approach to ipsilateral or bilateral neck dissection according to these findings. A more precise approach requires larger studies with more patients.

The relationship between the medial wall of pyriform sinuses involvement and lymphatic metastasis was not investigated in previous studies. In our study, 9 out of 16 patients (56%) with involved pyriform sinuses had lymphatic metastasis, and in 6 (37%) of them, lymphatic involvement was occult. The relation between pyriform sinuses involvement and lymph nodes metastasis was statistically significant.

The most accepted surgical approach for patients with supraglottic SCC is the selective dissection of level II-IV (1). Due to the low probability of level IV involvement and potential complications of level IV dissection such as pneumothorax and chylous fistula, more recent studies questioned routine dissection of level IV (11). Based on the results of these studies, in patients without involvement of level II and III (by frozen section analysis), routine dissection of level IV is not necessary. Single involvement of level IV in the absence of level II and III involvement was not seen in these studies (4,14-16). Our findings were consistent with these studies. Level II was the most frequently involved level, and single involvement of level IV was not seen, but unlike other studies, level IV was involved in one clinically N0 patient. Level IV involvement was associated with advanced disease, and none of the T2 patients had involvement in level IV. Regarding the above, dissection of level IV is recommended only in T3-T4 cases and in patients with involvement of level II or III. Less extensive surgery may reduce complications and costs.

In conclusion, supraglottic tumors have different nodal involvement patterns that differ based on T stage, histopathological grade, and site of involvement, so management should be adjusted accordingly. Although wider studies with more patients are needed to draw specific conclusions, our results suggest the possibility of

ignoring elective neck treatment in selected patients who are at low risk of having the occult nodal disease. Close follow-up should be considered in this group of patients.

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