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Original Research

Predictors of Cervical Lymph Node Metastasis in Patients with Squamous Cell Carcinoma of the Larynx

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Abstract

Objectives: In this retrospective study, we evaluated the effectiveness of the tumor volume, grade invasion depth in the prediction of cervical lymph node metastasis.

Identification of diagnostic parameters reliably predicting cervical lymph node involvement can be useful in improving the management of laryngeal cancer.

Methods: One hundred and seven patients with squamous cell carcinoma of larynx and who underwent surgery were assessed retrospectively. Age, sex, Tumor-Node-Metastasis (TNM) stage, grade, invasion depth and computerised tomography (CT) volume of the tumors were analysed. The association between these parameters and cervical lymph node metastasis was determined.

Results: Thirty two patients (29.91%) had positive cervical lymph nodes. Lymph node metastasis is detected in 13 (46.43%) poorly differentiated tumors, and in 19 (24.05%) moderate-well differentiated tumors. Mean volume was 2.15±0.14 cc in lymph node negative patients and 2.97±1.05 cc in lymph node positive patients. Mean invasion depth was 10.1±0.87 mm in lymph node negative patients and in 11.3±1.05 mm lymph node positive patients. The tumor grade and volume predicted successfully lymph node metastasis in patients with squamous cell carcinoma of the larynx, however invasion depth was not associated with nodal metastasis (p=0.047, p=0.0022, p=0.916, respectively).

Conclusion: The tumor grade and volume could predict cervical lymph node metastasis in patients with squamous cell carcinoma of the larynx, whereas the depth of invasion did not. Calculation of the tumor volume radiologically can help predict lymph node metastasis by minimizing the variability in measurements such as the depth of invasion.

Keywords: Larynx, lymph node, metastasis, squamous cell

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Laryngeal squamous cell carcinoma constitutes an important majority of head and neck tumors with an increasing mortality.[1] The Tumor-Node-Metastasis (TNM) classification and cervical lymph node metastasis are the most important prognostic factors.[2-5] Cigarette smoking, alcohol use, the extent of the surgical margin, cartilage invasion, keratin production, various mutations, ploidy, levels of the biomarkers and adhesion molecules are among the possible prognostic factors.[6,7]

Cervical lymph node involvement is an established risk factor for the distant metastasis.[7] Elective cervical lymph dissection (END) is advised during management of laryngeal cancer, especially if a patient has a high risk (>15-20%) of lymph node metastasis.[8,9] END can be helpful both diagnostically and therapeutically. Pathological examination can identify any need for adjuvant therapy and undetectable small metastatic foci can be removed.[8] Thus, identification of diagnostic parameters reliably predicting cervical lymph node involvement would aid clinicians in improving the management of laryngeal cancer.[9,10] The aim of the present study was to evaluate tumor volume, tumor grade, and the depth of invasion, as potential predictors of cervical lymph node metastasis.

Methods

The Patient Data

One hundred and seven patients with squamous cell carcinoma of larynx who underwent surgery were assessed retrospectively between 2019-23. The patients underwent partial or total laryngectomies and either elective or therapeutic bilateral neck dissections (49 total, 20 supraglottic, 5 supracricoid, 10 frontolateral, 1 vertical, 1 total frontoanterior, 13 total frontolateral, and 4 total supraglottic laryngectomies, 4 total cordectomies, and 99 bilateral selective (level II-IV, II-V, and I-V) neck dissections). The age, sex, TNM stage, tumor grade, tumor depth, and computed tomography (CT) tumor volumes were evaluated for each patient. The associations between these parameters and the extent of cervical lymph node metastasis were assessed.

Ethical approval obtained from the Istanbul Training and Research Hospital Clinical Research Ethics Committee approved the study (date: 26.05.2017, number: 1003) according to Helsinki Declaration.

Measurements

The American Joint Committee on Cancer (ACJJ) TNM (2010) classification was used for staging. We employed the widely used method of Moore et al.[11] to calculate tumor depth (the distance from the mucosal line to the deepest margin of the tumor). An ocular micrometer was used to this end (accuracy: 0.1 mm).

CT Evaluation

Contrast-enhanced CT scans of the head-and-neck were obtained using a Somatom Sensation 16 instrument (Siemens AG, Erlangen, Germany). The scan range in the axial plane ran from the skull base to the thoracic inlet. Reformatted images were reconstructed as coronal sections running vertical to the vocal cords, ranging from 1 cm above the hyoid bone to the inferior margin of the cricoid cartilage.

All images were retrieved from our picture archiving and communication system (PACS); the images were interpreted by two radiologists with ≥5 years of experience. Both radiologists were blinded to the clinical outcomes. The extent of cartilage invasion, tumor spread, and nodal involvement were assessed. A lymph node was scored as metastatic if necrosis and/or inhomogeneous enhancement were/was evident. Nodes of axial diameters >1 cm, and clusters of ≥3 lymph nodes with borderline features were regarded as malignant. tumoral borders on adjacent CT slices; tumor volumes were then calculated automatically by multiplying the total traced area by the reconstruction interval (Figs. 1, 2).

Statistical Analysis

Statistical analysis was performed with SPSS (ver.22.0, Chicago,USA). We used statistical tools to explore the associations between CT volume and other parameters relevant to cervical lymph node metastasis. ANOVA, student-t test and chi-squared test were used for statistical analysis. A p value less than 0.05 considered as significant. Tumor grade and depth of invasion was evaluated with ANOVA. A Chi-square test was used for the assessment of the extent of lymph node metastasis and tumor grade. The tumor volume and tumor grade was evaluated with ANOVA. The independent t-test was used for assessment of the relationship between the mean tumor volume and the lymph node positivity. The independent t-test was used for evaluation of the relationship between the mean tumor depth and the lymph node positivity. A chi-squared data was used for dividing patients into three groups according to their depth of tumor invasion.

Results

A total of 107 patients (males/females: 105/2) aged between 35-80 years were included. Of the tumors, 52 were in the supraglottic region, 12 in the transglottic region, and 43 in the glottic region. Of all tumors, 47 were early

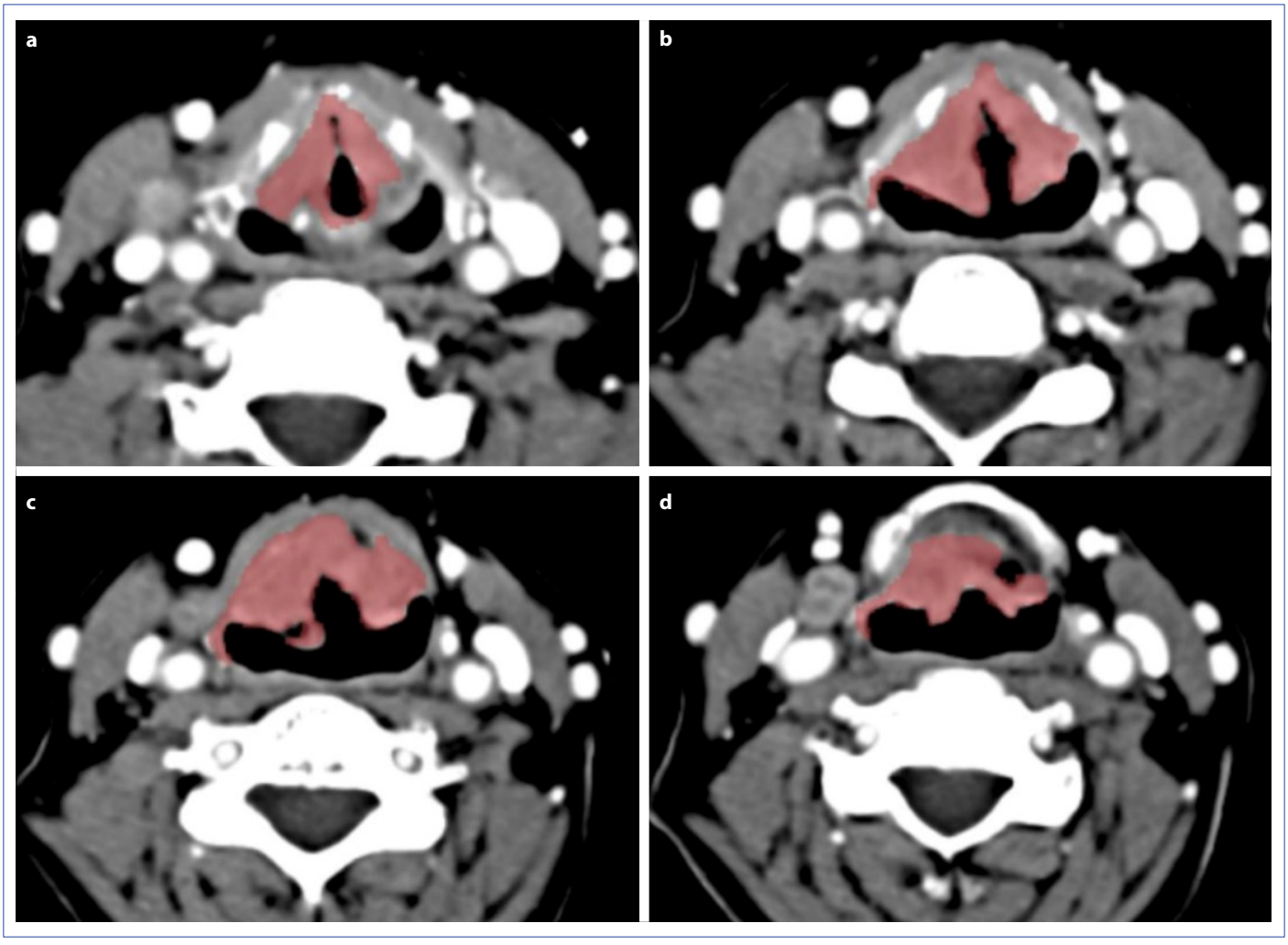

Figure 1. Four consecutive axial images of a supraglottic squamous cell carcinoma of larynx that causes preepiglottic and paraglottic invasion and aryepiglottic fold destruction, the tumor extends caudally to false cords level.

stage (T1-2) and 60 were advanced stage (T3-4). Cervical lymph node were positive in 32 (29.91%) patients. Lymph node metastasis was detected in 13 patients (46.43%) with poorly differentiated tumors, and in 19 (24.05%) of those with moderately to well-differentiated tumors.

The mean tumor volume was 1.49±0.29 cc in patients with well-differentiated tumors; 2.53±0.16 cc in those with moderately differentiated tumors; and 2.72±0.12 cc in those with poorly differentiated tumors. The mean tumor depth was 6.11±1.37 mm in patients with well-differentiated tumors; 10.12±0.76 mm in those with moderately differentiated tumors, and 13.29±1.69 mm in those with poorly differentiated tumors. There was a significant association between the tumor grade and depth of invasion (p=0.002). The extent of lymph node metastasis and tumor grade was significantly correlated (p=0.047). There was a significant association between the tumor volume and tumor grade (p=0.001) (Table 1).

The mean tumor volume was 2.15±0.14 cc in lymph node-negative patients and 2.97±1.05 cc in lymph node-positive patients. The mean tumor volume was significantly higher in lymph node-positive patients compared to lymph node-negative patients (p=0.001). In tumors <2.5 cc in volume, the extent of lymph node positivity was 16.1% and that of node negativity was 83.9%. In patients with tumors ≥2.5 cc in volume, the respective figures were 45.1% and 54.9%; the difference was significant (p=0.0022). The mean tumor depth was 10.1±0.87 mm in lymph node-negative patients and 11.3±1.05 mm in lymph node-positive patients. There was a statistically significant difference (p<0.005).

The included patients were divided into three groups according to their depth of tumor invasion. The first group contained patients with tumor depths >1 cm or <1 cm (the extent of lymph node positivity did not differ significantly between the two subgroups; p=1); the second group contained patients with tumor depths >1.5 cm or <1.5 cm (the

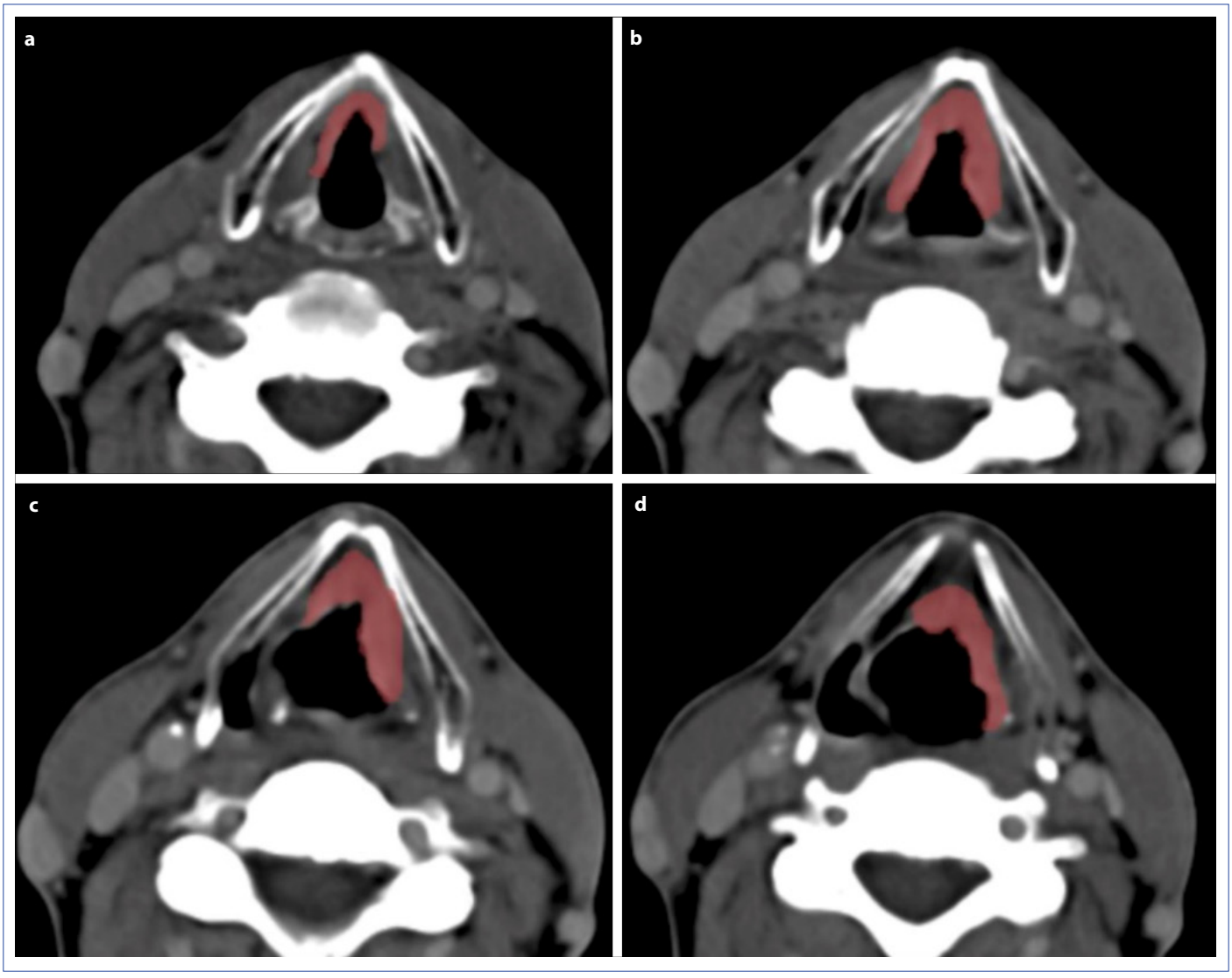

Figure 2. Four consecutive axial images of a transglottic squamous cell carcinoma of larynx that extends from aryepiglottic fold caudally to supracommissural level and invades anterior of bilateral true vocal cords.

Table 1. Relationship between differentiation, depth, and volume with extent of lymph node

	Differentiation		Depth (cm)		Volume (cc)	
	Well-Moderate	**Poor**	**<1**	**≥1**	**<2.5**	**≥2.5**
Lymph Node -	60 (75.95%)	15 (53.57%)	36 (70.6%)	39 (69.6%)	47 (83.9%)	28 (54.9%)
Lymph Node +	19 (24.05%)	13 (46.43%)	15 (29.4%)	17 (30.4%)	9 (16.1%)	23 (45.1%)
Total (N)	79	28	51	56	56	51

extent of lymph node positivity did not differ significantly between the two subgroups; p=0.645); and the third group had tumor depths >2 cm or <2 cm (the extent of lymph node positivity did not differ significantly between the two subgroups; p=0.347). Thus, these three groups did not differ significantly. Table 1 indicates the relationship between differentiation, depth, and volume with extent of lymph node and Table 2 indicates the relationship between volume and depth of invasion with tumor differentiation. The tumor grade and volume predicted successfully lymph node metastasis in patients with squamous cell carcinoma of the larynx, however invasion depth were not associated with nodal metastasis (p=0.047, p=0.0022, p=0.916, respectively) (Table 2).

Table 2. Relationship between volume and depth of invasion with tumor differentiation

	Differentiation		
	Well	Moderate	Poor
Volume (cc) Mean±SD	1.49±0.29	2.53±0.16	2.72±0.12
Depth (mm) Mean±SD	6.11±1.37	10.12±0.76	13.29±0.69

Discussion

Tumor stage at diagnosis is the most important predictor of survival and dictates treatment options.[12] Preoperative imaging techniques detect tumor-positive necks in all but 7.5% of patients. The 5-year survival rate is 29–54% in patients with nodal metastases versus 64–94.5% in non-metastatic patients.[13,14] Cervical lymph node metastasis increases the risk of distant metastasis, as does extracapsular extension; survival is thus compromised.[15] Laryngeal squamous cell cancer is histologically classified as well-differentiated (grade 1), moderately differentiated (grade 2), or poorly differentiated (grade 3). Small glottic tumors are often well-differentiated.[16-18] The grade is prognostically significant, but grading is subjective and affected by the sampling technique employed. Poorly differentiated or undifferentiated cancers are associated with poor prognoses.[19] However, the prognoses of patients with moderately and well-differentiated tumors did not differ significantly. Poorly differentiated cancers, especially supraglottic tumors, trigger lymphatic metastases more frequently.[19,20]

The histological grade influences the response to radiotherapy (RT), which affords better local control of tumors of grades 1 and 3 than of tumors with other grades. The rate of cervical metastasis for tumors >2 cm in diameter is 40%. The risk of local recurrence increases with tumor size in T1 glottic tumors treated via RT. Lower lip squamous cell carcinomas >2 cm in diameter frequently give rise to lymph node metastases.[21,22] Endophytic (inverted ulcerative) lesions infiltrate deeper into surrounding tissue. Ulceration of a primary carcinoma is negatively prognostic. Ulcerated supraglottic tumors metastasize to a greater extent than exophytic tumors. Yuen et al.[21] found that, in patients with tongue carcinoma, increased tumor thickness reduced 5-year disease-free survival and increased the risk of cervical metastasis and local recurrence.

Many recent studies have calculated pretreatment gross tumor volumes (GTVs) from CT scans; GTVs predict the prognoses of patients with nonsurgically treated carcinoma in different cervical subsites.[23] A larger tumor volume increases the risk (compared to a smaller volume) of local recurrence at the same anatomical site.[23-25] Increases in the GTVs of nasopharyngeal, oropharyngeal, and supraglottic carcinomas are associated with progressively reduced probabilities of local control.[23] Several studies have proposed that the association between GTV and local control is even stronger than that between tumor (T) stage and local control.[23-26]

GTV measurements also identify patients who would benefit from adjuvant chemotherapy. In patients at moderate risk of local recurrence after RT alone, the additional morbidity and toxicity associated with adjuvant chemotherapy may be objectively justified; the local control rate may be better when an RT/chemotherapy combination is prescribed.[24,25] Advanced-stage large-volume tumors are unlikely to respond to any form of combined nonsurgical therapy. Thus, volumetric data can be used for early identification of patients at high failure risk, triggering surgical intervention. This would limit the morbidity associated with delayed, unsuccessful combined therapy.

Yilmaz et al.[22]evaluated the significance of invasion depth in laryngeal cancer. And they found that invasion depth is related to metastasis free disease and long survival rate. In another study, depth of tumor invasion is highly associated with tumor location and diameter in laryngeal cancers.[26] Son et al.[27] assessed the success of tumor thickness as a predictive factor in showing recurrence of early glottic cancer in a study. They reported that the consideration of tumoral thickness, which is an important prognostic factor, before surgery is a guide for the extension of the tumor. In our study, however, no significant relationship was found between the depth of invasion and lymph node involvement. We think that the reason that we found such different results from the literature may be due to the presence of interobserver variability among pathologists. While absolute accuracy is based on the measurements in the pathology report, there are actually differences between pathological measurements depending on the pathologist. It is important to measure the volume of the tumor radiologically in order to prevent interobserver variability between pathologists and to have additional data in predicting lymph node metastasis.[28,29]

Conclusion

In conclusion, tumor grade and volume predicted cervical lymph node metastasis of squamous cell carcinoma of the larynx. Calculation of the tumor volume radiologically can help predict lymph node metastasis by minimizing the variability in measurements such as the depth of invasion.

Disclosures

Ethics Committee Approval: The Istanbul Training and Research Hospital Clinical Research Ethics Committee approved the study (date: 26.05.2017, number: 1003).

Authorship Contributions: Concept – A.S.M.; Design – D.R.; Supervision –O.M.; Fundings – Y.K.; Materials – F.Z.A.; Data collection &/ or processing – O.O.; Analysis and/or interpretation – G.A.K.; Literature search – F.Z.A.; Writing – O.O.; Critical review – G.A.K.

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