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Histopathologically Positive Regional Neck Node Metastasis Among Patients with Laryngeal Squamous Cell Carcinoma

ABSTRACT

Objective: To determine the patterns of regional neck node metastasis in laryngeal squamous cell carcinoma in Filipinos according to subsite and clinical stage and to determine possible factors associated with level V involvement.

Methods:

Design: Retrospective Case Series

Setting: Tertiary National University Hospital

Participants: A chart review was conducted for patients diagnosed with laryngeal squamous cell carcinoma who underwent laryngectomy with neck dissection from January 2011 to April 2015. Medical information obtained included demographics, clinical parameters and histopathologic reports of nodal involvement. The rate and location of positive neck nodes was recorded according to clinical stage and primary subsite. Fisher exact test was used to determine significant risk factors for level V cervical lymph node involvement.

Results: From the 56 patients included, most were male with an average age of 61 years. Most patients had cancer originating from the glottic subsite with the majority being staged III and IVA according to the TNM classification. Histopathologically, positive neck nodes were centered at levels II to IV. No significant association was seen between level V involvement and the studied clinicopathologic factors (age, sex, tumor differentiation, subsite involvement, involvement of other neck node levels).

Conclusion: Cervical neck node levels II, III and IV are the most commonly involved in neck dissection with many being positive for nodal metastasis for these levels. Level V nodes may be removed when clinically positive, but elective neck dissection may exclude this level. The current practice of neck dissection appears to be appropriate in terms of selecting the most likely locations of metastatic spread. Further study is recommended with a greater population and standardized levels of neck dissection.

Keywords: *laryngeal cancer, lymphatic metastasis, neck dissection, squamous cell carcinoma*

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The authors declare that this represents original material, that the manuscript has been read and approved by all the authors, that the requirements for authorship have been met by each author, and that each author believes that the manuscript represents honest work.

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Laryngeal squamous cell carcinoma is one of the less common cancers but has significant morbidity and mortality.¹ Treatment commonly involves concomitant partial or total laryngectomy with neck dissection.² Involvement of levels II, III and IV has been demonstrated in prior studies in other populations even for patients with N0 necks, supporting selective neck dissection for these levels.^{2,3} The study aims to provide a guide for management of laryngeal squamous cell carcinoma by describing the patterns of neck node metastasis in Filipinos and comparing it to data in other countries and determining possible factors associated with involvement of level V nodes. This may guide the determination of nodal subsites recommended for neck dissection during surgery according to the patient's clinical stage.

METHODS

With institutional review board approval, this retrospective study accessed the patient database of medical records of the Philippine General Hospital, University of the Philippines Manila. Records included charts from patient admissions at Ward 10, Department of Otorhinolaryngology, surgeries performed in the Right Central Block Operating Room Complex and histopathologic readings compiled at the Surgical Pathology Section, Department of Laboratories.

Records of patients aged 18 years old and above diagnosed with histopathologically-confirmed laryngeal squamous cell carcinoma, stage I-IV and admitted at the Department of Otorhinolaryngology charity ward of the Philippine General Hospital from January 2011 – April 2015, who underwent laryngeal surgery with neck dissection were considered for inclusion in the study. Following the department protocol for management of laryngeal cancer, patients were diagnosed with laryngeal squamous cell carcinoma with a minimum of a complete head and neck examination and direct laryngoscopy with biopsy proving the pathology. A contrast computed tomography (CT) scan of the larynx and neck was obtained in patients with T2, T3 and T4 tumors, all patients with mucosal or submucosal tumors, and those with suspected cervical nodal metastasis. Chest radiographs and liver function tests were also performed to rule out distant metastasis. Neck dissection was done according to each surgeon's judgment, guided but not dictated by the department protocol. For glottic and subglottic cancer, neck dissection is usually done for stage III or worse; and dissection of levels II to IV is done with inclusion of surrounding structures (such as the sternocleidomastoid, internal jugular vein, and spinal accessory nerve) as needed. For supraglottic cancer, no set guidelines were given for stage I and II necks but both sides were advised to be addressed surgically due to risk of occult metastasis. Suggested neck dissection for stage III and worse was the same as for

glottic cancer. Patients with unavailable or incomplete records were excluded from the study.

Data was collected for each patient regarding demographics and initial clinical impression in terms of stage and primary subsite. Post-operative records were reviewed to obtain surgical information on the laryngeal tumor and nodal involvement. Pertinent data obtained is summarized in the following table.

Table 1. Patient data and histopathologic results obtained

Patient Data	Histopathologic Results
Age	Tumor differentiation
Sex	Involved laryngeal subsites
Clinical stage (TNM)	Neck node levels dissected
Clinical primary subsite	Neck node levels with positive involvement Number of nodes involved

After obtaining the pertinent data, tabulation using MS Excel version 1803 (Build 9126.2152 Click-to-Run), (Microsoft Corporation, Redmond WA, USA) was done according to primary subsite and clinical stage for each patient to determine the levels of neck nodes dissected and levels with positive involvement. Descriptive statistics were used to summarize this and demographic data. To determine the association between level V nodal spread and the clinicopathologic factors (age, sex, tumor differentiation, primary subsite and involvement of other nodal levels), the Fisher exact test was done using SPSS Version 24, IBM 64-bit edition (IBM Corp, Armonk, NY, USA), with a p-value of less than .05 being considered significant.

RESULTS

Collection and tabulation of the patient database showed 185 patients in the census of patient admissions with suspicion or assessment of laryngeal malignancy for any purpose. Review of patient records narrowed the list of patients with available charts, diagnosed with laryngeal squamous cell carcinoma based on biopsy and treated with surgery that specifically included neck dissection to 56 patients (53 males, 3 females). Ages ranged from 40 to 77 years and the mean age was 61 years. Most patients presented with laryngeal cancer in the fifth decade of life (25 patients) followed by the sixth decade (18 patients) and seventh decade (10 patients).

In terms of primary subsite based on clinical history, physical examination and diagnostic tests, 46 had glottic involvement followed by 8 supraglottic and 2 subglottic. Using the TNM classification, most patients were staged III (11 patients) and IVA (40 patients).

Table 2. Rate of histopathologically positive neck node metastasis among patients with glottic primary subsite.

Glottic Primary Subsite							
Stage	# of Pts (n=46)	Level I n/subtotal (%)	Level II n/subtotal (%)	Level III n/subtotal (%)	Level IV n/subtotal (%)	Level V n/subtotal (%)	Level VI n/subtotal (%)
II	1		0/1 (0)	0/1 (0)	0/1 (0)		
III	9	1/2 (50)	2/8 (25)	2/8 (25)	2/8 (25)	1/4 (25)	1/1 (100)
IVA	33	0/5 (0)	10/33 (30)	10/33 (30)	9/33 (27)	1/14 (7)	2/6 (33)
IVB	3	1/1 (100)	2/3 (66)	3/3 (100)	1/3 (33)	0/1 (0)	

In the eight patients with supraglottic primary subsite involvement, 3 had level II involvement, 2 in level III and 1 in level IV. For the two patients with subglottic primary, one patient had involved nodes at levels I, II, III and IV. Distribution of histopathologically positive nodes for the 46 glottic patients is detailed in *Table 2*. Focusing on levels II to IV, 25 percent of neck nodes in stage III patients and approximately 30 percent in stage IV patients had positive involvement. Notably, this is despite all stage III glottic patients having been pre-operatively assessed as N0.

No statistically significant association was noted between level V involvement and any of the pre-operative patient characteristics, namely age ($p = .32$), sex ($p = 1.0$), primary subsite involved ($p = 1.0$), pre-operative clinical stage ($p = .12$), as well as post-operative histopathologic findings of tumor differentiation ($p = 1.0$), level II involvement ($p = .48$), level III involvement ($p = .21$) and level IV involvement ($p = .39$).

DISCUSSION

Cancer of the larynx is one of the less common cancers ranking at 21st total, 14th for men and 21st among women in 2010; incidence rises at age 50 for men and 70 for women.¹ The vast majority of laryngeal malignancies, more than 95 percent are squamous cell carcinomas.^{1,4} Extension into tributary lymph nodes is a well-known possibility in all neck cancers including malignant laryngeal tumors.² However, there is no general agreement on optimal elective neck dissection for glottic cancer, especially in clinically N0 patients.^{2,3} Limiting functional damage needs to be balanced with increasing the patient’s chance of survival.² In other populations, neck dissection of only levels II, III and IV has been shown to be comparable to more extensive neck dissections in terms of neck control, survival and accuracy of staging.³ However, no local studies have been found at present describing regional metastasis in laryngeal cancer or ideal treatment for such patients.

To address this deficit, our study aimed to document the current practice in our institution regarding neck dissection, as well as the

outcomes in terms of the likelihood of nodal metastasis contrasted with the frequency of dissection done per nodal level. This would help determine whether our institution is correctly balancing the need to maximize regional control and limit functional damage.

While the study is small in terms of population size, certain patterns and trends can be noted. Age and sex correlate well with existing local and international data that shows a greater risk of malignancy in age 50 and above and in men.^{1,7} Also consistent with prior data is the finding that the glottic subsite is the most commonly involved followed by the supraglottic area with the subglottic area rarely being the site of origin.⁷

In terms of TNM staging, it is notable that most patients involved were staged as IVA likely due to the specific criteria necessary to be included in the study. For patients with lower TNM stage, treatment may mostly involve radiotherapy and more conservative surgery for the larynx without necessarily including neck dissection unless with clinically apparent metastasis, hence exclusion from this study. For patients staged higher than IVA, definitive surgery may be seen as a less desirable and much riskier treatment option due to extensive primary involvement, nodal spread or distant metastasis; such patients would likely be treated with palliative radiotherapy instead. Accordingly, in our institution mostly patients staged III and IVA are perceived as benefitting from aggressive surgical treatment and neck node dissection due to the perceived risk of regional spread. This mode of thinking for treatment of laryngeal malignancies is in line with current guidelines that are based on TNM classification.⁵

While neck dissection is usually done for laryngeal squamous cell carcinoma, there is no general agreement regarding the best choice of nodal levels to involve,⁶ and this is apparent in our institution as well. The results of our study showed that levels II, III and IV are always included by surgeons in our institution in neck dissection for all primary subsites when doing total laryngectomy, regardless of T and N staging. Other levels are included only infrequently, selected in addition to levels II



to IV according to surgeon's preference, possibly because of clinically obvious or suspicious involvement. The lack of significant association between level V involvement and the clinicopathologic factors reviewed in this study would indicate that basing the surgical plan on these factors may be misleading. The low rate of level V involvement even in higher stages would support excluding dissection of this level except for clinically apparent involvement.

Due to the limited number of subjects, it is difficult to draw definite conclusions regarding the rate of nodal spread according to subsite, stage and neck node level. In general, significant risk of nodal spread is present in levels II to IV in all subsites even in clinically N0 patients but mostly in stage IVA and above. The high percentage of histopathologically involved nodes in certain other node levels - where neck dissection was seldom done - may be attributed to the selection of these nodes for surgery only in cases already with a high chance of positive results such as clinically enlarged nodes or involvement of other sites such as the thyroid gland.

Although the findings provide some insight into the effectiveness of our current practice, the small sample size and retrospective nature of this study prevent further analysis. More extensive study of the distribution of regional metastasis with laryngeal squamous cell carcinoma would ideally necessitate standardization of neck dissection to include all relevant neck node levels. Such a surgical practice would be difficult to defend ethically since only particular levels are known to be usually involved in most patients. The risk of involvement of levels I and V could, however, be measured indirectly in future studies by studying recurrence rates for these levels especially in patients who do not undergo post-operative irradiation. The predominance of high-staged lesions in this study with transglottic extension and bilateral involvement precludes determination of the ideal laterality of elective neck dissection – specifically, whether bilateral dissection is warranted for smaller masses isolated to one side.

Further investigation can be aimed at creating a more highly controlled, ideally prospective study with standardized neck node dissection with some levels aside from II, III and IV included as much as can be reasonably allowed by risk of nodal spread and concern for patient safety. A longer timeframe and a larger patient population, possibly involving several treatment centers may be included to allow for richer examination of the patterns of nodal metastasis. Patient status on follow-up could be assessed as well with study of rate of recurrence and location of recurrent nodal metastasis since local control is the critical hallmark of adequate neck dissection when doing therapeutic surgery. Comparison of post-operative histopathology with pre-operative diagnostics such as the CT scan may also be done

to determine their accuracy in predicting nodal involvement as a justification for using CT findings to determine selection of neck node levels for dissection.

This study suggests that in the patients studied, cervical neck node levels II, III and IV are the most commonly involved in neck dissection with many being positive for nodal metastasis for these levels. Our results suggest that the current practice of always including levels II, III and IV may be appropriate in anticipation of occult nodal metastasis even in patients with N0 necks. Due to the low number of patients who underwent neck dissection for levels I and V, it is difficult to say whether elective neck dissection is justified for these levels for any stage given the present data. However, many study factors limit the ability of the study to generalize to a larger population. The data collected from this study will ultimately serve not so much to affect surgical practice directly or immediately but as a basis for more extensive studies in the future. Further studies may include an examination of recurrence rates and patient status after follow up.

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