Evaluation of Diagnostic Accuracy of Cervical Palpation, Contrast Enhanced Multi-detector Computed Tomography, and Intraoperative Macroscopic Nodal Assessment of Cervical Lymph Node Metastasis of Head and Neck Squamous Cell Carcinoma in Filipinos: A Preliminary Study

Cesar Vincent L. Villafuerte III,[1] Alfredo Q.Y. Pontejos Jr.,[1] Lord Euclid Anthony S. Loreto,[2] Imarzen V. Elepaño,[2] Henri Sim Co[2] and Edilberto Joaquin V. Fragante Jr.[2]

[1]*Department of Otorhinolaryngology, College of Medicine and Philippine General Hospital, University of the Philippines Manila*
[2]*Department of Radiology, College of Medicine and Philippine General Hospital, University of the Philippines Manila*

ABSTRACT

Objectives. 1) To determine if there is an association between physical examination by cervical palpation, pre-operative contrast-enhanced multi-detector computed tomography (MDCT), and intraoperative lymph node assessment, with final histopathology in the evaluation of cervical lymph node metastasis in Filipino patients with squamous cell carcinoma of the head and neck. 2) To determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and likelihood ratios of cervical palpation, contrast enhanced MDCT, and intra-operative lymph node assessment compared with final histopathology in the evaluation of cervical lymph node metastasis in Filipino patients with squamous cell carcinoma of the head and neck.

Methods. *Study Design.* Retrospective; Cross-sectional. *Setting.* Tertiary Government Hospital Charity Section, Department of Otorhinolaryngology, Department of Radiology, Department of Pathology. *Participants, Patients or Population.* Retrospective chart review of all biopsy proven head and neck squamous cell carcinoma patients admitted at the charity ward of a Otorhinolaryngology Department from 2008-2010 who had documented admission physical examination, a pre-operative contrast enhanced multi-detector computed tomography (MDCT) scan of the neck done in the same institution within 20 days or less from date of surgery, and underwent neck dissection with appropriate cervical lymph node level specimen labeling with subsequent post-operative histopathologic evaluation of submitted specimens for neck node metastasis by the Pathology Department of the same institution. After set of exclusion criteria was applied, the analyzed sample included 82 lymph node level samples from 9 patients with head and neck Squamous Cell Carcinoma (SCCA).

Results. Pre-operative contrast enhanced MDCT, and intraoperative nodal assessment, were both significantly

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Corresponding author: Cesar Vincent L. Villafuerte III, MD
Department of Otorhinolaryngology
College of Medicine
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Telephone: +632 5548400
Email: clvillafuerte@up.edu.ph

correlated with the final histopathologic evaluation of neck node metastasis as evaluated with Fisher's Exact test (p = 0.00). Cervical palpation however was not able to show a significant association (p=0.099).

Cervical palpation had a sensitivity of 25.00% (8.33-52.59%), specificity of 90.91% (80.61-96.25%), NPV of 83.33 (72.30-90.73%), PPV of 40.00 (13.69-72.63%), accuracy of 78.05%, and a likelihood ratio of 3.33. Pre-operative contrast enhanced MDCT had a sensitivity of 43.75% (20.75-69.45%), specificity of 93.94% (84.44-98.04%), NPV of 87.32 (76.80-93.69%), , PPV of 63.64 (31.61-87.63%), accuracy of 84.15%, and a likelihood ratio of 12.06. Intraoperative surgical evaluation had a sensitivity of 68.75% (41.48-87.87%), specificity of 93.94% (84.44-98.04%), NPV of 92.54 (82.74-97.22%), PPV of 73.33 (44.83-91.09%), accuracy of 89.02%, and a likelihood ratio of 34.10.

Further analysis with McNemar's Test comparing MDCT and Intraoperative assessment showed no significant difference (p = 0.387).

Discussion and Conclusions. In the evaluation of cervical lymph node metastasis for head and neck squamous cell carcinoma in the local setting, the extent of neck dissection, clinical staging and prognosis, as well as adjuvant therapy can be guided by pre-operative contrast enhanced MDCT and intra-operative nodal assessment. Contrast-enhanced MDCT can aid treatment planning in preoperative or non-operative cases; but intraoperative evaluation can be used to guide final extent of surgery. Evaluation solely by physical examination by cervical palpation unfortunately in this study was not able to show a significant association with final histopathology.

Key Words: cervical lymph node metastasis, regional, head and neck, Squamous Cell Carcinoma, clinical, palpation, radiographic, Multi-detector Computed Tomography, surgery, histopathology, diagnostic accuracy, sensitivity and specificity

INTRODUCTION

Head and neck squamous cell carcinoma is reported to account for 5% of cancers worldwide with an over-all 5-year survival of less than 50%.[1] In the Philippines it was estimated to account for a total of 4982 new cancer cases, and 3354 cancer deaths in 2010.[2] One of the most important prognostic factors of head and neck Squamous Cell Carcinoma (SCCA) is the presence of lymph node metastasis, which has been shown to decrease survival by 50% for unilateral metastasis, and 25% for bilateral metastasis.[3]

The evaluation of malignant cervical lymph nodes remains a major challenge in the diagnosis and management of squamous cell carcinoma of the head and neck. Results regarding neck node detection through cervical lymph node palpation have been varied. Published reviews have demonstrated wide ranges in sensitivities for physical examination through cervical lymph node palpation ranging from 59.2%-83%, and specificities from 50-90%.[3,4] One report in particular has demonstrated neck node staging through cervical palpation to be inaccurate with the rate of occult nodal metastasis in N0 necks being at least 30%.[5]

As such, imaging modalities have gained wide usage for the pre-operative detection of cervical lymph node metastasis especially in the clinically N0 neck on physical examination. A recently published meta-analysis of imaging techniques for detection of cervical metastasis in N0 necks has pooled estimates of 52% (39-65%), 65% (34-87%), 66% (47-80%), and 66% (54-77%) sensitivity; and 93% (77-93%), 81% (64-91%), 87%(77-93%), and 78% (71-83%) specificity for multi-detector computed tomography (MDCT), magnetic resonance imaging (MRI), positron emission testing (PET), and ultrasound (US) respectively in the evaluation of head and neck SCCA cervical metastasis.[5]

In addition to physical examination by palpation and imaging, intra-operative nodal assessment has also been used to evaluate for possible cervical lymph node metastasis. Several studies have shown intra-operative cervical lymph node macroscopic assessment to have a sensitivity range of 41-56% and a specificity range of 57-70%.[4]

In the local setting the most commonly employed methods of assessing cervical lymph node status are often limited to pre-operative physical examination via cervical palpation, contrast enhanced MDCT, and intra-operative assessment of involved lymph nodes by the head and neck surgeon. The use of MRI and PET are limited due to prohibitive cost. While, MDCT supersedes US due to its greater capacity to include assessment of the primary tumor extent as well as more deeply situated nodes, such as retropharyngeal nodes - which would be difficult to access sonographically.

All of these are important because extent of neck dissection surgery is guided by lymph node status. Throughout the latter half of the last century, there has been a paradigm shift towards more conservative neck dissection surgeries - movements from radical to functional and selective neck dissection due to decreased risks for post-op morbidities.[6] Inclusion of cervical lymph node levels in neck dissection surgery is indicated when at least 20% rate for metastasis is found for that level from previously published patterns of neck metastasis for cancer head and neck cancer primary sub-sites, particularly in the N0 neck.[7,8]

Similar studies have postulated that in order to avoid unnecessary treatment of histologically negative cervical lymph node levels, an evaluation technique must be sensitive enough in order to reduce the risk of undetected

nodal metastasis to less than 20% - which would mean a negative predictive value of more than 80%.[5] The decision whether to include a cervical lymph node level in neck dissection will thus be affected by known rates of neck node level involvement per primary sub-site, as well as the pre-treatment evaluation of cervical node involvement.

Thus, the determination of the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and likelihood ratios from local experience using the most often utilized methods of evaluating cervical node metastasis would be an important aid in: (1) the decision making regarding extent of neck dissection and its corresponding risks for morbidities, (2) clinical staging and prognostication and (3) for pre-operative assessment regarding the need for possible adjuvant therapy in Filipinos with known head and neck primary SCCA. As stated previously, in the local setting this would include evaluation of physical examination by cervical palpation, contrast-enhanced pre-operative MDCT and intraoperative nodal assessment.

Hence the objectives of this study were:

1. To determine if there is a correlation between physical examination by cervical palpation, pre-operative contrast-enhanced multi-detector computed tomography, and intraoperative lymph node assessment with final histopathology in the evaluation of cervical lymph node metastasis in Filipino patients with squamous cell carcinoma of the head and neck.
2. To determine the sensitivity, specificity, positive predictive value, negative predictive value, accuracy, likelihood ratios of cervical palpation, contrast enhanced MDCT, and intra-operative lymph node assessment compared with final histopathology in the evaluation of cervical lymph node metastasis in Filipino patients with squamous cell carcinoma of the head and neck.

METHODS

A. Study Design

Retrospective; Cross-sectional

B. Setting

Tertiary Government Hospital Charity Section, Department of Otorhinolaryngology, Department of Radiology, Department of Pathology

C. Participants, Patients or Population

The population included all biopsy proven head and neck squamous cell carcinoma patients admitted at the charity ward of the Otorhinolaryngology Department of a tertiary government hospital in 2008-2010 who had documented admission physical examination, a pre-operative contrast enhanced multi-detector computed tomography (MDCT) scan of the neck done in the same institution within 20 days or less from date of surgery and underwent neck dissection with appropriate cervical lymph node level specimen labeling with subsequent post-operative histopathologic evaluation of submitted specimens for neck node metastasis by the Pathology Department of the same institution.

Out of 278 admitted head and neck SCCA patients, only 62 had their pre-operative CT-Scans done in the same institution, while only 27 of these patients had a post-operative histopathology result which included a neck dissection (with the rest containing mostly pre-operative biopsy results). Of these patients, only 9 had their operation within 20 days or less from the date of CT-Scan. Thus after the set of exclusion criteria was applied, the analyzed sample included only 82 lymph node level samples from 9 patients with head and neck SCCA.

D. Intervention or observation procedures

Chart review was done on all of the patients who fulfilled the inclusion criteria and patient information was tabulated accordingly. Admission physical examination records completed by otorhinolaryngology residents were used to identify clinical neck node positivity as evaluated through palpation. All the pre-operative MDCT scans were then reviewed by a radiology resident and a board-certified radiology consultant and each cervical lymph node level was evaluated for neck node positivity. Intra-operative neck node status was determined by chart review of neck dissection operative techniques with notation of surgically positive nodes as recorded by the surgeon. Neck dissection specimens were marked per neck node level to enable subsequent appropriate labeling on final histopathology which were signed out by board-certified pathologists. Since this is a retrospective study, blinding was not assured, however the evaluators who did the palpation, radiographic examination, intraoperative assessment, and pathologic determination typically worked separately with information supplied to the radiologist and pathologist through request forms containing basic history and physical examination data and clinical diagnosis.

E. Main and secondary outcome measures

Histopathologic positivity was determined by review of the final histopathologic reports with notation of cervical lymph node level positivity.

F. Data analysis and interpretation

Cervical palpation, contrast enhanced MDCT, intra-operative nodal assessment and histopathologic positivity were then tabulated and labeled accordingly per cervical lymph node level. These clinical, radiographic, and surgical data were compared with the reference standard of histopathologic positivity to determine their respective sensitivity, specificity, negative predictive value, positive predictive value, accuracy and likelihood ratios. (Appendices A, B, C).

RESULTS

A. Descriptive Data *(Table 1)*

Table 1.

	# of Patients	# of Nodes	Percent Nodal Representation
Age			
49	1	8	9.7%
52	2	23	28.0%
56	1	12	14.6%
58	2	20	24.4%
59	1	1	1.21%
64	1	14	17.0%
75	1	4	4.88%
Sex			
Male	7	64	78.0%
Female	2	18	22.0%
Site			
Buccal	1	8	9.7999.7%
Floor of Mouth	1	14	17%
Gingivobuccal	1	4	4.9%
Laryngeal (Glottic)	3	23	28.0%
Laryngeal (Supraglottic-Glottic)	1	12	14.6%
Lip	1	9	10.9%
Tongue	1	12	14.6%
Stage			
II	2	8	9.8%
III	2	25	30.5%
IVA	4	41	50.0%
IVB	1	8	9.8%
Tumor			
T2	2	9	11.0%
T3	3	38	46.3%
T4 unspecified	1	9	11.0%
T4A	2	18	22.0%
T4B	1	8	9.8%
Node			
N0	2	16	19.5%
N1	2	20	24.4%
N2	3	24	29.3%
N2B	1	8	9.8%
N2C	1	14	17.1%
Metastasis			
M0	9	82	100.0%

Investigators were able to examine 82 lymph node levels from 9 patients with biopsy-proven SCCA of the head and neck. Age distribution of patients was from 49-75. Two of the patients were female and 7 were male which translated to 18 node levels from females and 64 from males. Primary tumor sites were from the tongue, buccal, gingivobuccal, floor of mouth, lip, laryngeal (glottic), laryngeal (glottic-supraglottic) and laryngeal (transglottic). Cancer stages were from Stage II – IVB with TNM classifications ranging from T2-T4b and N0-N2c. No distant metastasis was detected in all of the patients who underwent surgery. Distribution of cervical lymph nodes evaluated were from levels IA (9; 10.9%), IB (11nodes; 13.4%), II (14 nodes; 17.1%), III (14 nodes; 17.1%), confluent II/III (2 nodes; 2%), IV (14 nodes; 17.1%), VA (9 nodes; 10.9%), and VB (9 nodes 10.9%). Of these, 16 (19.5%) neck node levels were noted to be pathologically positive for metastasis and 66 (80.5%) were negative.

B. Analytical Data

Pre-operative contrast enhanced MDCT, and intraoperative nodal assessment, were both significantly correlated with the final histopathologic evaluation of neck node metastasis as evaluated with Fisher's Exact test (p = 0.00) (Table 2). Cervical palpation however was not able to show a significant association (p=0.099). 95% Confidence intervals were also subsequently computed using vassarstats.net software (Tables 3 and 4).

Cervical palpation had a sensitivity of 25.00% (8.33-52.59%), specificity of 90.91% (80.61-96.25%), NPV of 83.33 (72.30-90.73%), PPV of 40.00 (13.69-72.63%), accuracy of 78.05%, and a likelihood ratio of 3.33. Pre-operative contrast enhanced MDCT had a sensitivity of 43.75% (20.75-69.45%), specificity of 93.94% (84.44-98.04%), NPV of 87.32 (76.80-93.69%), , PPV of 63.64 (31.61-87.63%), accuracy of 84.15%, and a likelihood ratio of 12.06. Intraoperative surgical evaluation had a sensitivity of 68.75% (41.48-87.87%), specificity of 93.94% (84.44-98.04%), NPV of 92.54 (82.74-97.22%), PPV of 73.33 (44.83-91.09%), accuracy of 89.02%, and a likelihood ratio of 34.10.

Further analysis with McNemar's Test comparing MDCT and intraoperative assessment showed no significant difference (p = 0.387) (Table 5).

DISCUSSION

The results of the study were able to demonstrate a significant association between contrast-enhanced MDCT and intraoperative nodal assessment with the gold standard of histopathology (p=0.00). Cervical nodal palpation however was not able to show the same significance in association (p=0.09).

Cervical nodal palpation had a sensitivity of 25.00% and specificity of 90.91%. The sensitivity noted in this study was lower than that reported in literature of 59.2%-83%. However, the specificity was within the reported range of 50%-90%. In turn, the positive predictive value of palpation was 40.00, accuracy 78.05% and the likelihood ratio was 3.33. Although the negative predictive value of clinical palpation of 83.33 was greater than the 80% cut-off for reduction of undetected nodal metastasis to less than 20%, this series was not able to show a significant association between palpation and histopathology. The study however may have been underpowered due to limited sample size. These findings however are consistent with the reported occult metastatic rate of >=30% for cervical palpation alone in N0 necks. As such relying purely on clinical palpation for

Table 2.

	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value	Accuracy	Odds Ratio	Fisher's Exact
Palpation	25.00	90.91	83.33	40	78.05	3.33	0.099
MDCT	43.75	93.94	87.32	63.64	84.15	12.06	0.000**
Intraoperative Evaluation	68.75	93.94	92.54	73.33	89.02	34.10	0.000**

***Significant to P value 0.05*

Table 3.

Method	Sensitivity	95% CI		Specificity	95% CI	
	Estimate	Lower	Upper	Estimate	Lower	Upper
Palpation	25.00%	8.33%	52.59%	90.91%	80.61%	96.25%
MDCT	43.75%	20.75%	69.45%	93.94%	84.44%	98.04%
Intra-operative Evaluation	68.75%	41.48%	87.87%	93.94%	84.44%	98.04%

Table 4.

Method	PPV	95% CI		NPV	95% CI	
	Estimate	Lower	Upper	Estimate	Lower	Upper
Palpation	40.00%	13.69%	72.63%	83.33%	72.30%	90.73%
MDCT	63.64%	31.61%	87.63%	87.32%	76.80%	93.69%
Intra-operative Evaluation	73.33%	44.83%	91.09%	92.54%	82.74%	97.22%

Table 5.

	Positive	Negative	Total
Positive	7	8	15
Negative	4	63	67
	11	71	82
McNemar Test Result			0.387695

decision-making regarding extent of neck dissection cannot be supported by this series.

Contrast-enhanced MDCT showed a sensitivity of 43.75% and specificity of 93.94% obtained from the study sample. These were both within the ranges reported in literature – sensitivity range of 39%-65% and specificity range of 77%-93%. Positive predictive value of 63.64, accuracy 84.15% and the likelihood ratio of 12.06 for contrast-enhanced MDCT were also obtained from this study sample. Negative predictive value was computed at 87.32%, which is above the 80% cut-off in reduction of undetected nodal metastasis to less than 20%. These along with the significant association of the sample with final histopathology shows the value of pre-operative contrast enhanced MDCT in the evaluation of cervical lymph node metastasis, and its effects in decision-making regarding extent of neck dissection, clinical staging and prognostication, and adjuvant treatment planning.

Intraoperative nodal assessment showed the highest sensitivity of 68.75%, positive predictive value of 73.33, accuracy of 89.02%, and likelihood ratio of 34.10. The specificity of 93.94% was equivalent to that of contrast-enhanced MDCT. The reported sensitivity and specificity in this series were higher than those previously reported ranges in literature - sensitivity 41-56%, specificity 57-70%. The negative predictive value of 93.94 was higher than the 80% cut-off and there was significant association between intraoperative assessment and histopathology.

Intraoperative nodal assessment had the best over-all performance values among the methods assessed in this study. However, there was no significant difference between contrast-enhanced MDCT and intraoperative nodal evaluation with p = 0.387695 using McNemar's Test.

This study shows that both preoperative MDCT and intraoperative nodal assessment were significantly associated with final histopathology. Intraoperative nodal assessment is a valid tool to guide the surgeon in extending planned extent of neck dissection if warranted by intraoperative findings. The drawback of this method however would be the fact that the patient would need to undergo operative exploration and its corresponding risks for this to be applied. It would not be applicable for patients who otherwise would not have undergone surgery and instead would undergo definitive radiotherapy with or without chemotherapy as treatment for nodal metastasis. This highlights the role of preoperative contrast enhanced MDCT as a preoperative evaluation technique. It has the benefit of being less invasive and can be done preoperatively to guide the surgeon regarding his operative plan, or the radiation or medical oncologist in cases where the patient would undergo non-surgical treatment. Cervical palpation in this study however unfortunately was not able to show significant association and cannot be recommended alone for evaluation of nodal status. In areas or circumstances where MDCT however is not available, palpation can still help guide operative plan and the addition of intraoperative nodal assessment can be used to decide the final extent of neck dissection.

Limitations

This study is limited by low sample size, predominance of higher stage cancers and low representation of clinical N0 necks. As a retrospective study utilizing

chart review it is also subject to the accuracy of the available patient documents.

Recommendations

Increasing sample size and subgroup analysis of N0 necks would be of value. A prospective study can also be done to further validate the initial findings from this report. Findings from this study can be used to develop a pre-operative, radiographic, and intraoperative form to be used for data gathering in a prospective study.

CONCLUSIONS

In the evaluation of cervical lymph node metastasis for head and neck squamous cell carcinoma the local setting - extent of neck dissection, clinical staging and prognosis, as well as adjuvant therapy can be guided by pre-operative contrast enhanced MDCT and intraoperative nodal assessment. The contrast-enhanced MDCT can aid treatment planning in preoperative or non-operative cases; but intraoperative evaluation can be used to guide final extent of surgery. Evaluation solely by physical examination by cervical palpation unfortunately in this study was not able to show a significant association with final histopathology.

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Statement of Authorship

All authors have approved the final version submitted.

Author Disclosure

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APPENDICES

Appendix A. Cervical Palpation + Histopathology Chi-Square

			Histopathology			
			Positive		Negative	
Physical Examination by Cervical Palpation	Positive	A	4	B	12	16
		Sensitivity	40.00			
		PPV	25.00			
	Negative	C	6	D	60	66
				Specificity	83.33	
				NPV	90.91	
			10		72	82
		Odds Ratio	3.33		Accuracy	78.05
			Fisher's exact = 0.099			

Appendix B. Contrast-enhanced MDCT + Histopathology Chi-Square

			Histopathology			
			Positive		Negative	
Contrast-enhanced MDCT	Positive	A	7	B	4	11
		SN	43.75			
		PPV	63.64			
	Negative	C	9	D	62	71
				SP	93.94	
				NPV	87.32	
			16		66	82
		Odds Ratio	12.06		Accuracy	84.15
			Fisher's exact = 0.000			

Appendix C. Intra-operative Nodal Evaluation + Histopathology Chi-Square

			Histopathology			
			Positive		Negative	
Intra-operative Nodal Evaluation	Positive	A	11	B	5	16
		SN	73.33			
		PPV	68.75			
	Negative	C	4	D	62	66
				SP	92.54	
				NPV	93.94	
			15		67	82
		Odds Ratio	34.10		Accuracy	89.02
			Fisher's exact = 0.000			