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HEAD AND NECK

Usefulness of radiologic examinations for diagnosing level VI lymph node metastasis in patients with laryngohypopharyngeal carcinoma

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Abstract The aim of this study was to estimate the usefulness of imaging modalities for diagnosing level VI lymph node metastasis in patients with laryngohypopharyngeal cancer. A retrospective review of 138 patients with squamous cell carcinoma of the larynx or hypopharynx who underwent central compartment neck dissection (CCND) was performed. Level VI metastasis occurred in 29 of 138 (21 %) patients. CT accuracy and sensitivity for level VI lymph node was 85.5 and 48.3 %, respectively. Respective values for MRI, US, and PET were 84.4 and 41.4 %, 87.7 and 44.8 %, and 81.2 and 34.5 %. CT combined with US demonstrated the best result in sensitivity (51.7 %) and negative predictive value (NPV) (88.1 %) compared to those of other imaging techniques. CT combined with US could improve sensitivity and NPV compared to CT or US alone. Considering cost-effectiveness and the highest results in all parameters compared to those of other combinations of imaging techniques, CT combined with US could be the best preoperative imaging modalities for evaluating laryngohypopharyngeal cancer. However, these imaging techniques are not absolutely reliable methods for detecting occult metastasis in the level VI due to high false-negative rates. Elective CCND should be considered in indicated patients (>N2b, T4), even if physical examinations and the radiologic findings of level VI nodes are negative.

Keywords Central compartment · Lymphatic metastasis · Laryngeal neoplasm · Hypopharyngeal neoplasm · Diagnostic imaging

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Introduction

The central compartment, also referred to as the anterior compartment of the neck, or cervical lymph node level VI, encompasses the prelaryngeal, pretracheal, paratracheal, and perithyroidal lymph nodes along the recurrent laryngeal nerve [1]. In squamous cell carcinoma (SCC) arising from the larynx, hypopharynx, and cervical esophagus, the central compartment lymph nodes may be at risk for lymph node metastasis [2]. The presence of metastasis in level VI has been implicated in the development of mediastinal, distant metastasis, and stomal recurrence [3, 4]. Furthermore, level VI metastasis with extranodal spread is an important adverse prognostic factor for disease-free and overall survival [5]. Therefore, it is important to estimate the status of level VI lymph nodes preoperatively, and to determine which patients are best suited for central compartment neck dissection (CCND).

There are no generally recognized guidelines for performing CCND for laryngeal, hypopharygeal, and cervical esophageal cancer. Therefore, the decision to perform CCND depends on the surgeon's preference, which in turn

is dictated by the surgeon's experience and results of diagnostic imaging techniques. More reliable diagnostic imaging modalities for the detection of occult level VI metastasis are necessary for the better selection of patients for CCND.

The aim of this study was to evaluate the usefulness of imaging modalities for diagnosing level VI metastasis in patients with laryngohypopharyngeal carcinoma by comparing the results of preoperative imaging using computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), and positron emission tomography (PET) with postoperative pathologic findings following neck dissection.

Patients and methods

Patients

The records of 475 patients who received surgical treatment for larynx or hypopharynx cancer at the Ilsong Memorial Head and Neck-Thyroid Cancer Hospital, Hallym University College of Medicine, from 2004 through 2013 were retrospectively identified and reviewed. Patients who did not undergo CCND ($n = 304$), insufficient data ($n = 4$) and salvage cases ($n = 29$) were excluded. Consequently, a total of 138 patients with laryngohypopharyngeal SCC who underwent CCND were retrospectively analyzed in this study. CCND was performed when there was any radiological evidence of level VI lymphadenopathy or potential risk of occult metastasis (T3/T4, subglottic extension, pyriform sinus apex invasion, postcricoid invasion, or extralaryngeal extension). Positive preoperative image was defined as radiologically positive finding of level VI nodes using any imaging modality (CT, MRI, US, or PET). Twenty-three patients (16.7 %) underwent CCND based on the positive preoperative image of level VI (cN+, level VI) and 115 patients (83.3 %) underwent CCND based on the potential risk of occult metastasis of level VI (cN0).

The study group consisted of 128 men and 10 women (mean age 64 years; range 43–88 years). Fifty-two patients were diagnosed with a laryngeal carcinoma and 86 patients had a hypopharyngeal carcinoma. T1, T2, T3, and T4 pathological stage was diagnosed in 0 (0 %), 15 (10.9 %), 44 (31.9 %), and 79 (57.2 %) patients, respectively. N0, N1, N2, and N3 disease stage of the cervical lymph nodes was evident in 26 (18.8 %), 16 (11.6 %), 89 (64.5 %), and 7 (5.1 %) cases, respectively (Table 1).

Table 1 Patient characteristics

N	All patients 138	Larynx 52	Hypopharynx 86
Age (years)			
Mean (range)	64 (43–88)	64 (43–88)	65 (48–86)
Sex (%)			
Male	128 (93)	47 (90.4)	81 (94.2)
Female	10 (7)	5 (9.6)	5 (5.8)
T stage (%)			
T1	0 (0)	0 (0)	0 (0)
T2	15 (10.9)	6 (11.5)	9 (10.5)
T3	44 (31.9)	20 (38.5)	24 (27.9)
T4	79 (57.2)	26 (50.0)	53 (61.6)
N stage (%)			
N0	26 (18.8)	10 (19.2)	16 (18.6)
N1	16 (11.6)	8 (15.4)	8 (9.3)
N2a	9 (6.5)	8 (15.4)	1 (1.2)
N2b	49 (35.5)	13 (25)	36 (41.9)
N2c	31 (22.5)	13 (25)	18 (20.9)
N3	7 (5.1)	0 (0)	7 (8.1)

Patient data

CT, MRI, US, and PET images were interpreted by one experienced head and neck radiologist. The levels and boundaries that were used were based on previously reported radiological definitions [6]. A level VI node was considered to be positive for metastasis if it was spherical shape, or showed an abnormal density or enhancement, or was significantly asymmetric compared with the contralateral side [7, 8]. The presence of central necrosis, and the localized group of nodes were also considered metastasis [7, 8]. ^{18}F-FDG uptake was expressed as the maximum standardized uptake value (max SUV) corrected for the injected radioactivity and patient body weight. Only hypermetabolic lesions with strong focal uptake (max SUV > 2.5) were considered metastasis. Pathological reports regarding level VI lymph node were reviewed. Radiologist's interpretation of preoperative CT, MRI, US, and PET, and the results from the pathologic analysis of the dissected level VI lymph nodes were compared to assess sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the accuracy of each imaging method.

Technique of CCND

All patients underwent primary tumor resection in combination with ipsilateral CCND with curative intent. CCND was performed cranial to the hyoid bone, caudal to the innominate artery, lateral to the carotid sheaths, and dorsal to the prevertebral fascia [1, 9]. CCND included the removal of the thyroid lobe on the involved side. Total thyroidectomy with bilateral CCND was performed when there was definite radiological evidence of thyroidal

invasion. The CCND specimens were labeled separately and sent for histological examinations.

Statistical analysis

The sensitivity, specificity, PPV, NPV, and accuracy associated with CT, MRI, US, and PET were calculated using standard definitions. These values of CT, MRI, US, and PET were compared using the McNemar's test. A p value <0.05 indicated a statistically significant difference.

Results

Prevalence of level VI metastasis

Among the 138 patients, 23 patients (16.7 %) underwent CCND based on the positive preoperative image of level VI (cN+, level VI) and 115 patients (83.3 %) underwent CCND based on the potential risk of occult metastasis of level VI (cN0). Of the 23 cN+ patients, 15 were true-positives and 8 were false-positives. Of the 115 cN0 (level VI), 14 were false-negatives and 101 were true-negatives. Consequently, among the 138 patients, level VI metastasis (pN+) was confirmed by pathologic analysis in 29 patients (21 %), comprising 15 cN+ patients and 14 cN0 patient (Fig. 1). The primary site of the 29 pN+ patients was the larynx in 7 and the hypopharynx in 22. The rate of level VI metastasis was 21 % (29 pN+ of 138), comprising 13.5 % (7 of 52) for laryngeal carcinoma and 25.6 % (22 of 86) for hypopharyngeal carcinoma. The prevalence of level VI metastasis was higher among patients with hypopharyngeal cancer than laryngeal cancer.

The rate of overall occult level VI metastasis was 12.2 % (pN+ out of cN0, 14 of 115); 7 % (3 of 43) for laryngeal carcinoma and 14.9 % (11 of 74) for hypopharyngeal carcinoma.

Of 29 pN+ patients, 24 patients (82.8 %) showed multiple lymph nodes metastasis (>N2b). Only five patients (17.2 %) showed single level VI lymph node metastasis (N1). However, these five patients had stage T4 cancer (Table 2). Among these five patients, four patients had hypopharyngeal cancer invading the pyriform sinus apex or thyroid cartilage, and one patient had laryngeal cancer which had subglottic extension.

Diagnostic value of CT, MRI, US, and PET for detecting level VI metastasis

The results of the pathologic analysis of the dissected level VI lymph nodes were compared with the radiologist's interpretation. The sensitivity, specificity, PPV, NPV, and overall accuracy of CT for detecting level VI metastasis was 48.3, 95.4, 72.2, 87.4, and 85.5 %, respectively. The respective values for MRI were 41.4, 96.3, 75, 86.1, and 84.8 %.The respective values for US were 44.8, 99.1, 92.9, 87.1, and 87.7 %. PET showed relatively lower sensitivity, specificity, PPV, NPV, and accuracy compared to CT, MRI, or US (34.5, 93.6, 58.8, 84.3, and 81.2 %; Table 3). PET showed significantly lower specificity compared to US (99.1 vs 93.6 %; $p = 0.031$). CT demonstrated the highest

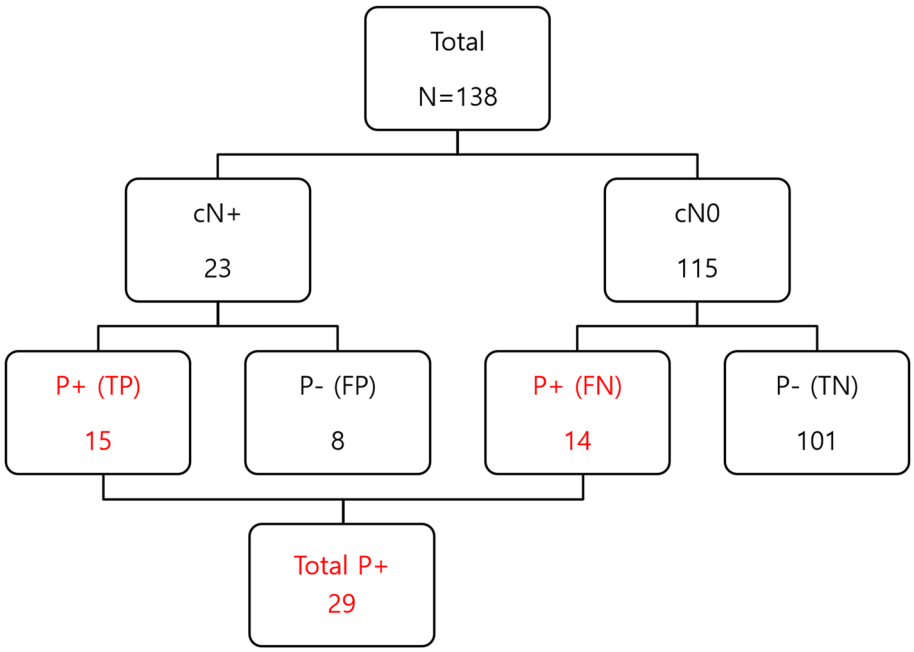

Fig. 1 Schematic view of the results. Of the 138 patients, 23 underwent CCND based on the positive preoperative image of the level VI (cN+) and 115 patients underwent CCND based on the potential risk of occult metastasis of level VI (cN0). Of the 23 cN+ patients, 15 were true-positives. Of the 115 cN0, 14 were false-negatives. Consequently, 29 patients were confirmed as level VI metastasis (P+) by pathologic analysis. *P+* pathologically confirmed level VI metastasis, *P−* pathologically negative of level VI, *TP* true positive, *FP* false positive, *FN* false negative, *TN* true negative

Table 2 Pathologic staging for the 29 level VI positive patients

Stage	N0	N1	N2a	N2b	N2c	N3	Total (larynx/hypopharynx)
T1	–	–	–	–	–	–	0
T2	–	–	–	3	–	1	4 (1/3)
T3	–	–	–	2	2	–	4 (2/2)
T4	–	5	–	8	8	–	21 (4/17)
Total (larynx/hypopharynx)	0	5 (1/4)	0	13 (3/10)	10 (3/7)	1 (0/1)	29 (7/22)

Table 3 Correlation of CT, MRI, US, and PET results with pathological proven level VI metastasis

Imaging	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
CT	14	5	15	104	48.3	95.4	72.2	87.4	85.5
MRI	12	4	17	105	41.4	96.3	75.0	86.1	84.8
US	13	1	16	108	44.8	**99.1**	**92.9**	87.1	**87.7**
PET	10	7	19	102	34.5	93.6*	58.8	84.3	81.2
CT + MRI	14	6	15	103	48.3	94.5	70.0	87.3	84.8
CT + US	15	5	14	104	**51.7**	95.4	75.0	**88.1**	86.2
CT + PET	14	7	15	102	48.3	93.6	66.7	87.2	84.1
MRI + US	14	6	15	103	48.3	94.5	70.0	87.3	84.8
MRI + PET	13	8	16	101	44.8	92.7	61.9	86.3	82.6
US + PET	13	7	16	102	44.8	93.6	68.3	86.4	83.3

Bold values indicate the hightest value of each category

CT computed tomography, *MRI* magnetic resonance imaging, *US* ultrasonography, *PET* positron emission tomography, *TP* true positive, *FP* false positive, *FN* false negative, *TN* true negative, *PPV* positive predictive value, *NPV* negative predictive value

* PET showed significantly lower specificity compared to US ($p = 0.031$)

sensitivity and NPV compared to those of MRI, US, and PET. US demonstrated the best specificity, PPV, and accuracy for detecting level VI metastasis. The most common radiological misdiagnosis in this study was false-negative. The false negative rate was 48.3 % in CT, 58.6 % in MRI, 55.2 % in US, and 65.5 % in PET (Fig. 2). The false positive rate was 4.6 % in CT, 3.7 % in MRI, 0.9 % in US, and 6.4 % in PET.

The sensitivity, specificity, PPV, NPV, and overall accuracy of CT combined with US (CT/US) for detecting level VI metastasis was 51.7, 95.4, 75, 88.1, and 86.2 %, respectively. US improved sensitivity, PPV, NPV and accuracy compared to CT alone. The respective values for MRI combined with US (MRI/US) were 48.3, 94.5, 70.0, 87.3, and 84.8 %. US improved the sensitivity and NPV compared to MRI. PET combined with US (PET/US) showed higher results in sensitivity, PPV, NPV, and accuracy compared to PET. MRI in addition to CT (CT/MRI) had a sensitivity of 48.3 %, specificity of 94.5 %, PPV of 70.0 %, NPV of 87.3 %, and an accuracy of 84.8 %. CT/US demonstrated the highest results in all parameters compared to those of other combinations of imaging techniques. However, there were no statistical differences (Table 3).

Discussion

The prevalence of level VI metastasis differs in various studies. Previous studies reported 21–26 % of patients with laryngeal, hypopharyngeal carcinomas had level VI metastasis [2, 3, 5, 13]. In this study, overall prevalence of level VI metastasis was 21 % (29 of 138) among all cases, comprising 13.5 % (7 of 52) for laryngeal carcinoma, and 25.6 % (22 of 86) for hypopharyngeal carcinoma, which is within the previously reported range. The overall prevalence of occult level VI metastasis in this study was 12.2 % (14 of 115), comprising 7 % (3 of 43) for laryngeal carcinoma and 14.9 % (11 of 74) for hypopharyngeal carcinoma. Management of clinically negative lymph nodes is controversial. However, these patients usually undergo elective neck treatment when occult lymph node metastasis is very likely (greater than 15–20 %) [10, 11]. Result from our study suggested that elective CCND is not mandatory in clinically negative level VI lymph nodes.

In this study, of 29 pN+ patients, 24 patients (82.8 %) showed multiple lymph nodes metastasis (>N2b). Five patients (17.2 %) showed single level VI lymph node metastasis (N1), however, these patients had stage T4 cancer (invasion of pyriform sinus apex or thyroid

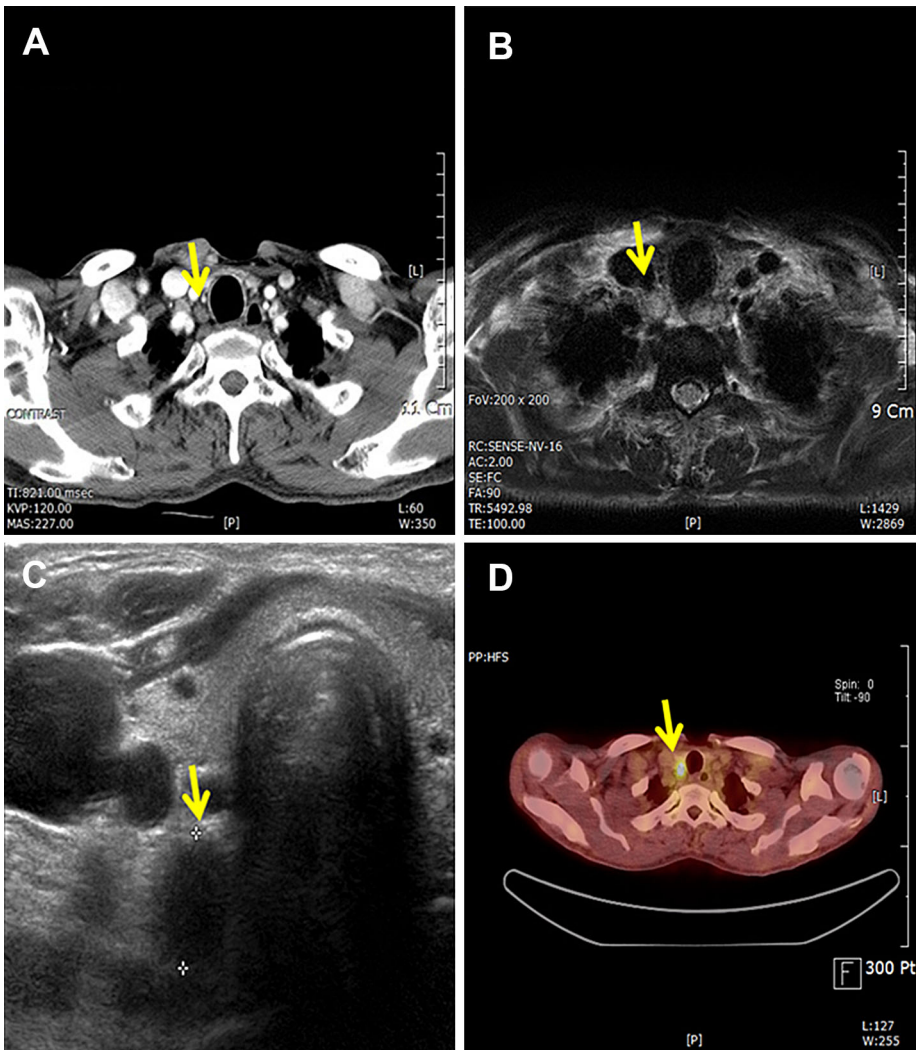

Fig. 2 True-positive CT, MRI, US, and PET results for a pathologic level VI metastasis. A 52-year-old male patient demonstrated an approximately 1.5 cm enlarged lymph node (*arrow*) in level VI on contrast-enhanced CT (**a**), MRI (**b**), US (**c**). PET also showed increased ^{18}F-FDG uptake (max SUV 14.8) in the level VI region (**d**)

cartilage, subglottic extension). Some studies have suggested that ipsilateral CCND should be performed as part of selective neck dissection in all patients with tumors invading the sublottis, pyriform sinus apex, and postcrioid region [12, 13]. In addition, the presence of positive lymph nodes at cervical level I–V may pose a significantly greater risk of developing level VI metastasis [5, 9, 13]. This study also indicates that patients with multiple lymph nodes metastasis and T4 cancer are at a greater risk of level VI metastasis. Therefore, elective CCND should be considered in indicated patients (>N2b, or T4) even if physical examinations and the radiologic findings of level VI nodes are negative.

The imaging modalities of cervical lymph nodes in level I–V have been extensively studied. However, there have been few studies of imaging techniques for the detection of level VI metastasis [11–15]. Peters et al. reported the sensitivity and specificity of CT for the detection of PTLN metastasis are as low as 70 and 36 %, respectively, and those of MRI are 50 and 71 % [14]. Kim et al. reported PET/CT and CT/MRI demonstrated low sensitivity for detecting level VI metastasis (58, 42 %) [9]. In this study, CT/US demonstrated the best result in sensitivity (51.7 %) and NPV (88.1 %) compared to those of other imaging techniques. CT combined with US could improve sensitivity and NPV compared to CT or US alone. Considering cost-effectiveness and the highest results in all parameters compared to those of other combinations of imaging techniques, CT combined with US could be the best preoperative imaging modalities for evaluating laryngohypopharyngeal cancer.

In addition, all parameters of PET in the detection of metastatic level VI lymph nodes were unfavorable compared to those values of the other imaging modalities (CT, MRI, and US). Also, PET showed significantly lower specificity compared to US. Result from our study suggested that PET has limited diagnostic performance in the evaluation of level VI metastasis in patients with laryngeal

or hypopharyngeal SCC. Additionally, CT/MRI had an accuracy of 84.8 %, which was lower than CT alone (85.5 %). This result suggests that performing MRI in addition to CT does not improve the diagnostic accuracy in detection of level VI metastasis in patients with laryngo-hypopharygeal SCC. The false negative rate of CT, MRI, US, and PET obtained from this study were 48.3, 58.6, 55.2, 65.5 %, respectively. These results suggested that diagnostic imaging modalities, such as CT, MRI, US, and PET, are not reliable for detecting occult metastasis in level VI lymph nodes.

Conclusion

In conclusion, CT combined with US could be the best preoperative imaging modalities for evaluating laryngo-hypopharyngeal cancer. Elective CCND could be avoided in clinically negative level VI lymph nodes. However, imaging techniques are not absolutely reliable methods for detecting occult metastasis in the level VI due to high false-negative rates. Therefore, elective CCND should be considered in indicated patients (>N2b, T4). In addition, routine intraoperative exploration of the level VI area and performing frozen biopsy should be considered for the treatment of >N2b or T4 cancer patients.

Compliance with ethical standards

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Conflict of interest Authors declares that he/she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

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