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Detection of Occult Primary Tumors in
Patients with Cervical Metastases of
Unknown Primary Tumors: Comparison
of Three-Dimensional THRIVE MR
Techniques with Two-Dimensional
Spin-Echo MR or Contrast-Enhanced
CT Imaging

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Spin-Echo MR or Contrast-Enhanced
CT Imaging

Directed by Professor Jinna Kim

The Master's Thesis
submitted to the Department of Medicine
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

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June 2017

This certifies that the Master's Thesis
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ABSTRACT

Detection of Occult Primary Tumors in Patients with Cervical Metastases of Unknown Primary Tumors: Comparison of Three-Dimensional THRIVE MR Techniques with Two-Dimensional Spin-Echo MR or Contrast-Enhanced CT Imaging

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Objective: We evaluated and compared the utility of postcontrast three-dimensional (3D) T1-weighted high resolution isotropic volume examination (THRIVE), spin-echo (SE) T1-weighted MR, and contrast-enhanced CT imaging for detecting occult primary tumors in patients with cervical lymph node metastases.

Materials and Methods: Seventy-three consecutive patients with tumors that went undetected during endoscopic or physical examinations underwent preoperative contrast-enhanced CT and MR imaging (SE and 3D THRIVE) after gadolinium injection. Guided biopsy or surgery results served as reference standards. The diagnostic performances of the imaging techniques were compared with McNemar's tests.

Results: Primary tumors were identified in 59 (80.8%) of the 73 patients after surgery. Of these, 36 were found in the palatine tonsil, 11 in the

base of the tongue, seven in the nasopharynx, and five in the pyriform sinus. The sensitivity (72.9%) and accuracy (71.2%) of 3D THRIVE for detecting primary tumors were higher than were those of SE T1-weighted MR (49.2% and 53.4%, $P \leq 0.002$) or CT (36.4% and 46.4%, $P \leq 0.001$). The specificities of these techniques did not differ. The diagnostic performance of 3D THRIVE (area under the curve [AUC] = 0.681) for detecting tumors did not differ from that of SE T1-weighted MR or CT (AUC = 0.671 and 0.608, $P > 0.05$).

Conclusion: 3D THRIVE was more sensitive at detecting primary tumors than was SE T1-weighted MR or CT imaging in patients with cervical metastases of unknown primary tumors; this sequence may improve biopsy and therapeutic planning in these patients.

Key words : carcinoma, cervical lymph node metastasis, unknown primary, magnetic resonance imaging, 3D THRIVE

Detection of Occult Primary Tumors in Patients with Cervical Metastases
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I. INTRODUCTION

When a primary tumor cannot be identified in a patient with biopsy-proven cervical lymph node metastasis despite thorough clinical examinations, it is defined as cervical lymph node metastasis from unknown primary tumors¹. Such patients should undergo endoscopic examinations of the upper aerodigestive tract during the initial clinical evaluation because accurate preoperative localization of the primary tumor in head and neck squamous cell carcinoma is a prerequisite for selecting appropriate treatment plans and predicting patients' prognoses¹⁻³. In addition, preoperative cross-sectional imaging has become mandatory to ensure accurate localization of the primary tumor^{4,5}.

Magnetic resonance (MR) imaging has been widely used in pre- and postoperative evaluations of patients with head and neck cancer because it provides excellent tissue contrast between the tumor and the surrounding structures⁶⁻⁸. It was previously reported that the T1-weighted high resolution isotropic volume examination (THRIVE) sequence, a three-dimensional (3D) ultrafast spoiled gradient MR sequence that incorporates a frequency-selective

fat-saturation pulse, may serve as an efficient alternative to the two-dimensional (2D) spin-echo (SE) T1-weighted MR sequence, as it provides more detailed anatomic information and good spatial resolution with reduced artifacts for preoperative head and neck cancer staging⁹. On the basis of this information, in the present study, we aimed to investigate and compared the clinical usefulness of the postcontrast THRIVE sequence, SE T1-weighted sequence, and contrast-enhanced computed tomography (CT) for the preoperative localization of occult primary tumors in patients with cervical lymph node metastasis.

II. MATERIALS AND METHODS

1. Patients

This retrospective study was approved by the institutional review board, which waived the requirement for informed consent. Between January 2011 and December 2016, 86 consecutive patients who initially presented with palpable lumps in the neck that were confirmed to be metastatic squamous cell carcinoma by fine-needle aspiration or biopsy of the cervical lymph nodes, but in whom primary tumors were not detected by full physical and endoscopic evaluations of the upper aerodigestive tract, were enrolled for this study. All patients underwent CT and/or MR imaging of the neck 2–4 weeks prior to panendoscopy and guided biopsy of the tonsils, base of the tongue, nasopharynx, hypopharynx, and any other sites suspected to harbor primary tumors. Patients were excluded for the following reasons: treated previously for head and neck cancer ($n = 6$), did not undergo preoperative MR imaging ($n = 2$), and did not undergo MR imaging with the required sequences ($n = 5$). Therefore, a total of 73 patients (61 men and 12 women; median age: 57 years; range: 33–79 years) who underwent both 3D THRIVE and 2D SE T1-weighted MR imaging were

included in this study. Of the 73 patients, four did not undergo preoperative CT examinations.

2. Image acquisition

Contrast material-enhanced CT examinations were performed on one of two CT scanners (Somatom Sensation 16 or 64; Siemens, Erlangen, Germany) using a standardized CT protocol for the neck. Contiguous 3-mm scans of the neck were acquired in the axial plane from the skull base to the carina, and then coronal images were reformatted at 2- to 3-mm increments. A total of 80–100 mL of the contrast agent iopromide (Ultravist 300; Bayer Schering Pharma, Berlin, Germany) was administered intravenously at a rate of 3 mL/s using an automated injector. Contrast material-enhanced images were obtained at 40–60 s after the initiation of contrast agent administration.

All patients underwent MR imaging with a 3.0-Tesla system (Intera Achieva or Achieva TX; Philips Medical Systems, Best, Netherlands) and a head and neck coil. Conventional MR imaging consisting of axial SE T1-weighted and fat-saturated axial fast SE T2-weighted imaging was performed according to our routine protocol for the head and neck area with a repetition time/echo time (TR/TE) of 560 ms/10 ms and 6480 ms/70 ms, respectively, before injecting the contrast material. All images were obtained with a 22–25 cm field of view, which was adjusted for each patient. Then, gadopentetate dimeglumine (Magnevist; Bayer Schering Pharma) was administered intravenously at a dose of 0.2 mL/kg body weight at a rate of 2 mL/s. Forty seconds after administering the contrast material, we first acquired fat-saturated axial THRIVE images, followed by fat-saturated axial and coronal SE T1-weighted images sequentially. The axial THRIVE images were then reformatted into the coronal and sagittal planes.

The sequence parameters for the fat-saturated SE T1-weighted images were

as follows: TR, 400–550 ms; TE, 10 ms; flip angle, 90°; bandwidth, 75.3 Hz/pixel; matrix, 256 × 256; section thickness, 4 mm; intersection gap, 1 mm; signal average, 2; and acquisition time, 303 s for axial images and 175 s for coronal images. The parameters for the fat-saturated 3D THRIVE images were as follows: TR, 4.5 ms; TE, 2.2 ms; flip angle, 10°; bandwidth, 434 Hz/pixel; matrix, 256 × 256; section thickness, 1 mm; signal average, 2; and acquisition time, 223 s.

3. Image interpretation

The CT and MR images were visually assessed and suspicious occult primary lesions were recorded by two experienced head and neck radiologists who were blinded to the patients' histories and final histopathologic results. The two radiologists assessed the CT and MR image series in a random fashion. Localization of the primary lesions was scored on a four-point scale, as follows: 0, no visible lesion; 1, equivocal visibility, rather likely pseudo lesion; 2, equivocal visibility, rather likely true lesion; and 3, visible lesion. Scores of 2 and 3 indicated tumor involvement. Disagreements between the two radiologists were resolved by consensus for the final evaluation. Suspicious primary lesions were confirmed through endoscopy-guided biopsy or surgery performed with general anesthesia, and the results served as the reference standard. This was followed by immunohistochemistry, wherein the human papillomavirus (HPV) status was determined by the overexpression of p16 protein, which is closely correlated with the HPV positivity^{10,11}.

4. Statistical analysis

The radiologists' scores for detecting occult primary tumors on postcontrast 3D THRIVE, postcontrast SE T1-weighted, and contrast-enhanced CT images were compared with the histopathologic results. The sensitivity, specificity,

accuracy, and positive and negative predictive values of each imaging method for identifying primary tumors were calculated with 95% confidence intervals and compared using McNemar's tests. To compare the diagnostic performance of each imaging modality, receiver operating characteristic curves were generated using a four-point scale, and the area under the receiver operating characteristic curve (AUC) was calculated. Pairwise comparisons of the AUCs were performed using DeLong method. To compare the size of tumors with false negative and true positive THRIVE results, Mann Whitney U-test was used. All statistical analyses were performed with the MedCalc software for Windows, version 17.2 (MedCalc Software, Ostend, Belgium), and SPSS for IBM, version 23.0 (SPSS, Chicago, IL). Statistical significance was set at $P < 0.05$.

III. RESULTS

The clinical characteristics of the 73 included patients are listed in Table 1. Forty (54.8%) of the 73 patients showed single level involvement of the metastatic lymph nodes, while 33 patients (45.2%) had multiple level involvement. Except for the two patients who presented with metastatic lymph node involvement in level I and III, respectively, all of the other patients showed level II involvement.

Table 1. Patient characteristics

Variable	No. of Patients (n = 73)
Sex	
Male	61 (83.6)
Female	12 (16.4)
Age (year) ^a	57 (33-79)
Metastatic cervical lymph node	
Side	
Right	39 (53.4)
Left	30 (41.1)
Both	4 (5.5)
Single level involvement	40 (54.8)
Multiple level involvement	33 (45.2)
Level II involvement	71 (97.3)
Primary tumor	
Site	
Palatine tonsil	36
Base of tongue	11
Nasopharynx	7
Pyriform sinus	5
Unknown	14
Size (mm) ^a	16 (3-34)
T stage	
T0 ^b	14 (19.2)
T1	43 (58.9)
T2	16 (21.9)
p16	
Positive	33 (75.0)
Negative	11 (25.0)
Unavailable	29

Note—Data are presented as the number of patients with percentages in parentheses unless otherwise noted.

^aData are medians with the range in parentheses.

^bPrimary tumor was not found during the final histopathological examination.

The final histopathologic examinations that were performed after guided biopsy or surgery according to the CT and MR imaging findings revealed that primary tumors were found in 59 (80.8%) of the 73 patients. Primary tumors were most frequently found in the palatine tonsil ($n = 36$), followed by the base of the tongue ($n = 11$), nasopharynx ($n = 7$), and pyriform sinus ($n = 5$). The median size of the tumors was 16 mm (range: 3–34 mm), with 43 T1 tumors and 16 T2 tumors. In the remaining 14 (19.2%) patients, primary tumors could not be detected despite thorough endoscopic evaluations and guided biopsies.

Immunohistochemistry for p16 was performed in 44 patients, and 33 (75%) of them showed positive results. Among the eight patients in whom primary tumors were not found during the final histopathological examination and in whom immunohistochemistry for p16 was performed, four patients (50%) showed positive results.

The postcontrast 3D THRIVE sequence enabled us to identify 43 (72.9%) of the 59 primary tumors, while postcontrast SE T1-weighted MR and contrast-enhanced CT enabled us to identify 29 (49.2%; $P = 0.001$ vs. 3D THRIVE) and 20 (36.4%; $P < 0.001$ vs. 3D THRIVE) of the 59 primary tumors, respectively. Postcontrast 3D THRIVE, postcontrast SE T1-weighted MR, and contrast-enhanced CT enabled us to correctly report the absence of tumors in nine (64.3%), 10 (71.4%), and 12 (85.7%) of the 16 tumors with unknown primary origin ($P > 0.05$), respectively. The diagnostic accuracy of 3D THRIVE (71.2%) was higher than were the accuracies of SE T1-weighted MR (53.4%; $P = 0.002$) and contrast-enhanced CT (46.4%; $P = 0.001$) (Table 2).

Table 2. Comparison of postcontrast 3D THRIVE, SE T1-weighted MR and CT imaging in the detection of primary tumors

Imaging technique and statistics	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	
3D THRIVE	43	5	16	9	72.9	64.3	71.2	89.6	36.0	
SE T1	29	4	30	10	49.2	71.4	53.4	87.9	25.0	
CT	20	3	35	12	36.4	85.7	46.4	90.9	25.5	
<i>P</i> value										
3D THRIVE vs. CT					< 0.001	0.250	0.001			
3D THRIVE vs. SE T1					0.001	1.000	0.002			

Note—3D THRIVE = three-dimensional T1-weighted high resolution isotropic volume examination, SE = spin echo, TP = true positive, FP = false positive, FN = false negative, TN = true negative, PPV = positive predictive value, NPV = negative predictive value.

The receiver operating characteristic analysis revealed that the diagnostic performance of the postcontrast 3D THRIVE sequence (AUC = 0.681; 95% confidence interval, 0.558–0.788) was higher than was those of SE T1-weighted MR (AUC = 0.671; 95% confidence interval, 0.548–0.780) and contrast-enhanced CT (AUC = 0.608; 95% confidence interval, 0.483–0.724), although the differences were not significantly different ($P = 0.865$ and $P = 0.357$, respectively) (Figure 1).

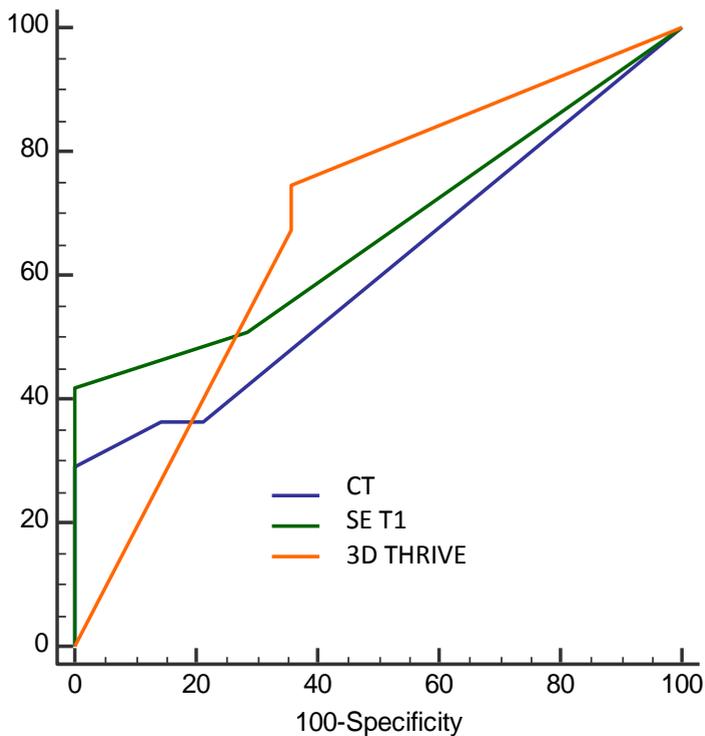


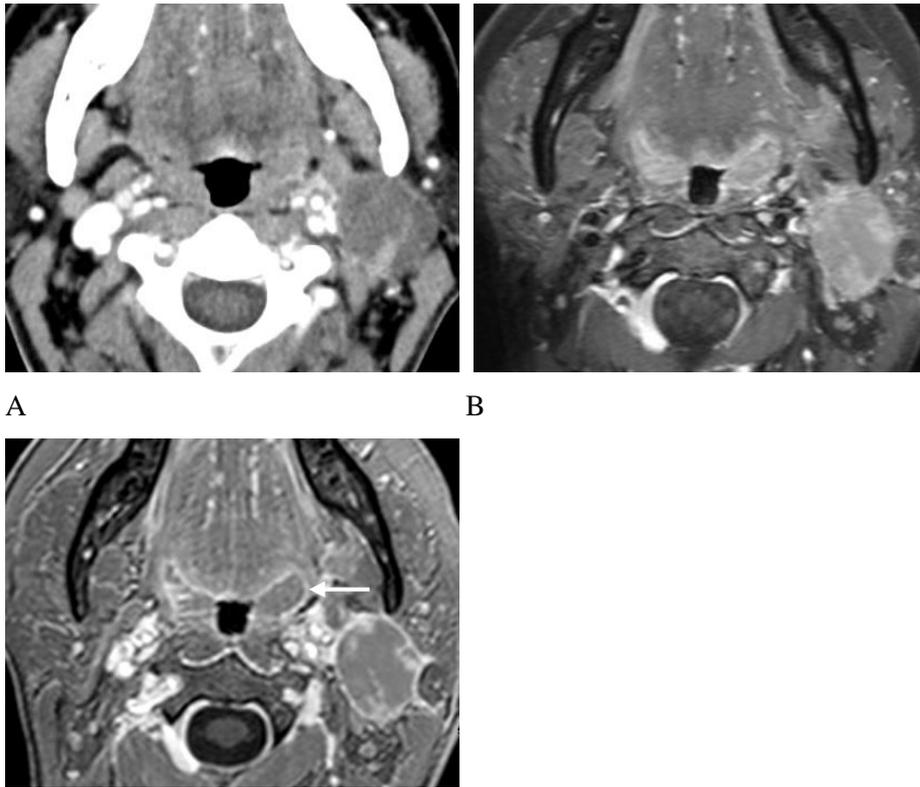
Figure 1. Receiver operating curve analysis comparing the diagnostic performance of postcontrast three-dimensional T1-weighted high resolution isotropic volume examination (3D THRIVE), spin-echo T1-weighted (SE T1) MR, and contrast-enhanced CT imaging.

The results of the 3D THRIVE and SE T1-weighted MR sequences in terms of their ability to detect primary tumors are summarized in Table 3. We found that 3D THRIVE yielded false-negative results in 16 patients, although primary tumors were identified in the palatine tonsil ($n = 7$), base of the tongue ($n = 6$), pyriform sinus ($n = 2$), and nasopharynx ($n = 1$). The overall median size of the primary tumors in patients with false-negative results from the 3D THRIVE sequence was 10 mm, which was much smaller than was that of the primary tumors in patients with true-positive 3D THRIVE results (median: 18 mm; $P = 0.013$). Representative 3D THRIVE, SE T1-weighted MR, and contrast-enhanced CT images are shown in Figures 2–4.

Table 3. Results of 3D THRIVE and SE T1-weighted MR imaging in the detection of primary tumors

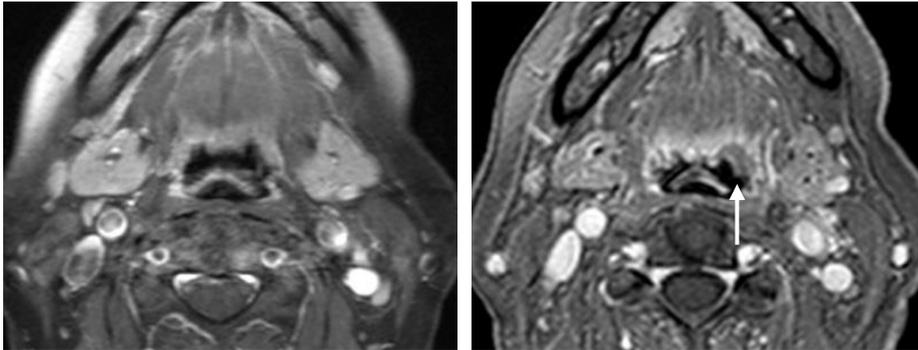
Primary site	Positive confirmed	TP		FP		FN		TN	
		3D TH	SE T1						
Palatine tonsil	36	29	24	0	0	7	12	0	0
Base of tongue	11	5	3	0	0	6	8	0	0
Nasopharynx	7	6	1	0	0	1	4	0	0
Pyriiform sinus	5	3	1	0	0	2	6	0	0
Unknown	14	0	0	5	4	0	0	9	10
Total	73	43	29	5	4	16	30	9	10

Note—3D TH = three-dimensional T1-weighted high resolution isotropic volume examination, SE = spin echo, TP = true positive, FP = false positive, FN = false negative, TN = true negative.



C

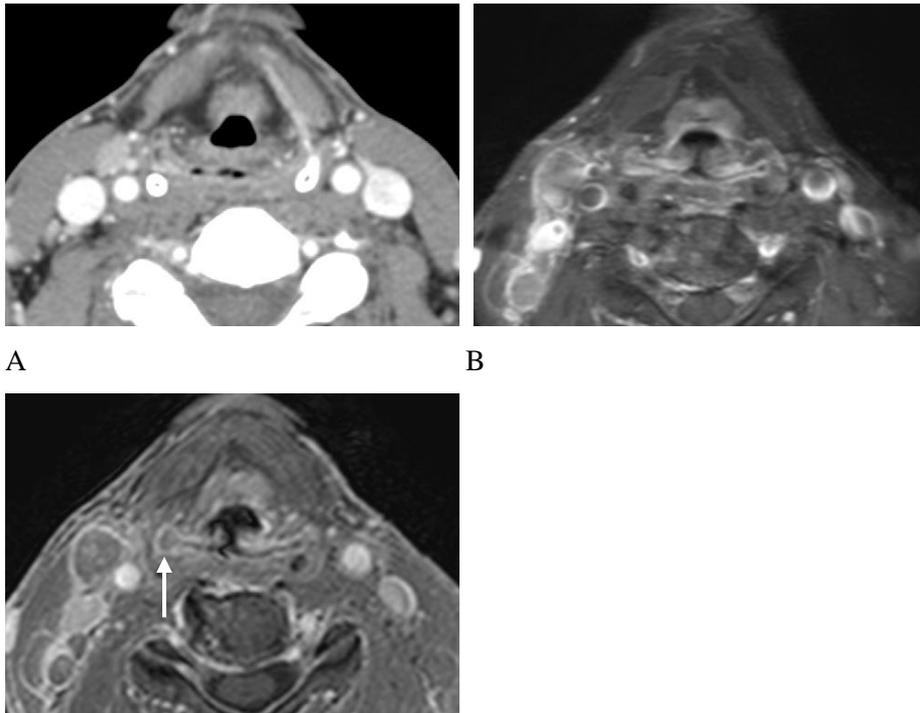
Figure 2. Delineation of the primary tumor in a 44-year-old woman with left tonsil cancer and metastatic cervical lymph nodes. Contrast-enhanced CT (A) and T1-weighted gadolinium-enhanced MR images (B) show mild asymmetric enlargement of the left tonsillar fossa. Postcontrast T1-weighted high resolution isotropic volume examination MR image (C) reveals more apparent delineation of the primary tumor with obliteration of the tonsillar crypts in the left palatine tonsil (arrow).



A

B

Figure 3. Detection of the primary tumor in a 54-year-old woman with cancer in the left base of the tongue and metastatic cervical lymph nodes. Contrast-enhanced T1-weighted MR image (A) shows no detectable primary tumor. Postcontrast T1-weighted high resolution isotropic volume examination MR image (B) reveals a suspicious primary tumor in the left base of the tongue (arrow), which was confirmed by targeted biopsy and histopathological examination.



C

Figure 4. Detection of the primary tumor in a 60-year-old man with right pyriform sinus cancer and metastatic cervical lymph nodes. CT (A) and T1-weighted MR images (B) show suspicious localized mucosal thickening in the right pyriform sinus. T1-weighted high resolution isotropic volume examination MR image (C) reveals better delineation of the primary tumor showing relatively poor contrast enhancement in the right pyriform sinus (arrow).

IV. DISCUSSION

In the present study, we compared the abilities of 3D THRIVE, SE T1-weighted MR, and contrast-enhanced CT imaging to depict occult primary tumors in 73 patients and used the biopsy or surgery results as the reference standard. Our data showed that the maximum detection rate of occult primary tumors was 73%. The diagnostic performance of the 3D THRIVE sequence was superior to those of SE T1-weighted MR and contrast-enhanced CT, as 3D THRIVE had higher sensitivity and accuracy for detecting primary tumors. However, the AUCs of these techniques were not significantly different. The major advantage of 3D imaging with isotropic data acquisition is that it does not show the partial volume averaging artifacts that are frequently observed on 2D images, and thus, 3D imaging provides smaller section thicknesses and higher spatial resolution for detecting small enhancing lesions in the head and neck area. In addition, images can be reformatted in any plane, which can simplify imaging protocols and reduce acquisition time⁹. Therefore, the 3D THRIVE sequence, which provides satisfactory image quality for primary tumor depiction, may be an acceptable alternative to SE T1-weighted MR or contrast-enhanced CT for preoperative evaluations in patients with metastatic cervical lymph nodes from unknown primary tumors.

Identifying occult primary tumors in patients with cervical lymph node metastases is still difficult when using conventional CT and MR imaging owing to technical challenges, including low image resolution and artifacts resulting from dental prostheses or air in the head and neck areas. Although various efforts to overcome these limitations during imaging evaluations of patients with cervical lymph node metastases from unknown primary tumors have been made, the detection rate of occult primary tumors with existing imaging techniques is reportedly ~37%¹². While fluorodeoxyglucose (FDG) positron

emission tomography (PET) has been commonly regarded as a next imaging modality for primary tumor detection in many institutions as it shows similar or slightly better sensitivity over cross-sectional imaging, PET has still major innate limitations such as additional use of radioactive tracers, low image resolution, and high false-positive results owing to inflammatory or infectious conditions, predominantly in the tonsils and nasopharynx¹³⁻¹⁵. If more detailed MR images are presented with PET images, it would be easier to distinguish false positive from true positive lesions. Moreover, if more masses are visualized in MR images, less patients will undergo PET. Therefore, more delicate anatomic imaging techniques or algorithms are needed to improve diagnostic performance for detecting primary tumors and to reduce the extent of invasive diagnostic procedures.

The proper identification of occult primary tumors in patients with cervical lymph node metastases is important for ensuring adequate surgical resection and tumor delineation for radiation therapy, which may result in improved treatment outcomes and reduced treatment-associated morbidity¹⁶⁻¹⁹. Furthermore, knowing the primary tumor site is critical for applying the appropriate post-treatment follow-up guidelines. Therefore, here, we focused on the sensitivity of several imaging modalities and sequences, since primary tumors that are overlooked or untreated may increase the risk of local recurrence.

For clinicians who perform endoscopy and biopsy, it is critical, but not always easy, to delineate primary tumor foci, even for large tumors, that may be hidden or embedded in normal lymphoid tissues or in the mucosa of the upper aerodigestive tract. Indeed, it was difficult for us to delineate tumors on the images we obtained, especially when symmetric enlargement of the bilateral tonsillar tissue with lymphoid hyperplasia was observed. Sixteen patients had false-negative results when the preoperative assessments were performed with the 3D THRIVE sequence. In these patients, tumors were

found frequently in the oropharynx, i.e., palatine tonsil, followed by the base of the tongue, and the primary tumors in patients with false-negative results were significantly smaller than were those from patients with true-positive results. Furthermore, in this study, 75.0% (33/44) of the patients in whom immunohistochemistry for p16 was performed showed positive results, and half (4/8) of the patients in whom occult primary tumors were not found had HPV-mediated tumors. According to the rapidly rising incidence of HPV-mediated oropharyngeal cancer, recent research has indicated that HPV-mediated tumors are commonly clinically/radiologically occult and are readily overlooked²⁰⁻²⁴. Therefore, radiologists must recognize this common clinical and radiologic pitfall of HPV-mediated oropharyngeal cancer, especially during evaluations of patients with cervical lymph node metastases from unknown primary tumors. Additionally, according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system for head and neck cancer, in patients with cervical metastasis of an unknown primary tumor, it should be acknowledged that the N category is designated according to a different nodal staging system that is based on HPV status, while the primary T category is described as T0²⁵.

Our study has several limitations. First, the time interval between the SE and 3D THRIVE scans in our protocol might have affected the results; that is, after contrast material injection, we obtained the 3D THRIVE sequence first followed by the SE sequence, without randomizing this order. As the total acquisition time for 3D THRIVE was approximately 4 min, differences in the gadolinium concentration might have affected the degree of enhancement and subsequently the diagnostic performance of each sequence. Second, completely blinded interpretations of the MR sequences were not possible because SE and 3D THRIVE are easily distinguishable by experienced reviewers. Finally, we did not include treatment and survival data, and such data might be necessary to

determine whether the diagnostic performance of each imaging modality influences the treatment outcome and patient survival. Further studies focusing on patient outcomes are needed.

V. CONCLUSION

The 3D THRIVE sequence is more sensitive at detecting primary tumors than is SE T1-weighted MR imaging or contrast-enhanced CT in patients with cervical lymph node metastases of unknown primary tumors. Collectively, our findings may improve biopsy targeting and therapeutic planning in patients with cervical lymph node metastases of unknown primary tumors.

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ABSTRACT(IN KOREAN)

원발병소 불명 경부 림프절 전이암 환자에서 원발병소 확인:
3차원 THRIVE 자기공명영상, 2차원 스핀에코 자기공명영상,
컴퓨터 단층촬영의 임상적 유용성 비교

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유 문 규

목적: 원발병소 불명 경부 림프절 전이암 환자에서 잠재적 원발
종양을 발견하기 위한 목적으로 조영증강 3차원 T1 강조
고해상도 등방성 체적 검사 (three-dimensional T1-weighted high
resolution isotropic volume examination, 3D THRIVE) 자기공명
시퀀스의 유용성을 스핀에코 T1 강조 자기공명영상 및 컴퓨터
단층촬영과 비교 평가한다.

연구방법: 경부 림프절 전이암이 확인되었으나 신체검사와
내시경 검사상 원발병소가 발견되지 않은 73명의 환자를
대상으로 하였다. 모든 환자들은 수술 전 조영증강 컴퓨터
단층촬영과 자기공명영상을 촬영하였으며 자기공명영상에는 3D
THRIVE와 스핀에코 T1 강조 영상이 포함되었다. 조직검사나
수술에서 얻은 병리 결과를 참조 표준으로 설정하였다. 각
검사의 진단적 유용성은 McNemar 검사를 이용하여 비교하였다.

결과: 수술 후 73 명의 환자 중 59 명 (80.8 %)에서 원발성

종양이 확인되었으며, 구개편도에서 36 개, 설기저에서 11 개, 비강인두에서 7 개, 이상와에서 5 개가 각각 관찰되었다. 원발병소를 찾는 데 있어서 3D THRIVE의 민감도 (72.9 %)와 정확도 (71.2 %)는 스핀에코 T1 강조 영상 (49.2 % and 53.4 %, $P \leq 0.002$)과 컴퓨터 단층촬영(36.4 % and 46.4 %, $P \leq 0.001$) 보다 높았으며, 특이도는 세 검사에서 유의미한 차이를 보이지 않았다. 수신자 조작 특성 곡선상 3D THRIVE의 진단적 유용성은 (AUC = 0.681) 스핀에코 T1 강조 영상, 컴퓨터 단층촬영과 유의미한 차이가 없었다 (AUC = 0.671 and 0.608, $P > 0.05$).

결론: 3D THRIVE 자기공명 시퀀스는 원발병소 불명 경부 림프절 전이암 환자의 잠재적 원발 종양을 발견하는 데 있어서 스핀에코 T1 강조영상이나 컴퓨터 단층촬영보다 더 예민한 검사로서, 조직검사의 표적 설정과 적절한 치료계획을 수립하는데 도움이 될 것으로 기대한다.

핵심되는 말 : 암종, 경부 림프절 전이, 원발병소 불명,
자기공명영상, 3D THRIVE