

Treatment Outcomes of Patients with Head and Neck Squamous Cell Carcinoma of Unknown Primary

Kyeong Suk Park, Hye Rin Lim, Se Hyun Jeong, Dong Hoon Lee*, and Sang Chul Lim

Department of Otolaryngology-Head and Neck Surgery, Chonnam National University Medical School & Hwasun Hospital, Hwasun, Korea

The purpose of this study was to evaluate clinical characteristics and treatment outcome of patients with head and neck squamous cell carcinoma of unknown primary (HNSCCUP), treated according to the method of our hospital. Six patients with histopathologically and radiologically confirmed HNSCCUP January 2010-December 2016 were enrolled in this study. All patients underwent radical neck dissection involving level I-V, bilateral tonsillectomy, and diagnostic esophagoscopy and postoperative radiotherapy (RT), with or without concurrent chemotherapy. There were no major complications resulting from surgical intervention. Duration of follow-up was 56.3 ± 20.2 months (range, 28-82 months). There was no recurrence or late detection of primary site of HNSCCUP. All patients with HNSCCUP except one were alive, at the time of the last follow-up. The other patient had no recurrence of HNSCCUP, but died of colon cancer at 58 months postoperatively. We have successfully treated patients with HNSCCUP by performing radical neck dissection, bilateral tonsillectomy, and diagnostic esophagoscopy and postoperative RT with concurrent chemotherapy, and recommend using this method as the main treatment method.

Key Words: *Unknown Primary Neoplasms; Squamous Cell Carcinoma; Neck Dissection; Radiation Oncology*

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Head and neck squamous cell carcinoma of unknown primary (HNSCCUP) is the presence of a cervical metastatic lymph node, whose primary site cannot be found on extensive clinical and radiological examinations.¹⁻³ Despite adequate diagnostic workup, incidence of head and neck carcinoma of unknown primary is approximately 2-7% of all neck masses.^{1,3,4} Since the primary site is unknown, the patient may be frightened of recurrence and uncertain progression.⁵

Treatment methods for HNSCCUP vary between centers, and treatment modalities include surgery with postoperative radiotherapy (RT), and RT with or without chemotherapy, followed by surgery.¹⁻⁶ At our institution, the preferred treatment of HNSCCUP is surgery, including radical neck dissection, bilateral tonsillectomy, diagnostic esophagoscopy, followed by RT with concurrent chemo-

therapy.

The purpose of this study was to evaluate clinical characteristics and treatment outcomes of patients with HNSCCUP, treated according to the preferred method of our hospital.

MATERIALS AND METHODS

This study was performed after obtaining approval from the Institutional Review Board of Chonnam National University Hwasun Hospital. Retrospectively, six patients with histopathologically and radiologically confirmed HNSCCUP from January 2010-December 2016, were enrolled in this study.

Inclusion criteria was patients with a histologically proven HNSCC from one or more affected lymph nodes of an unknown primary who underwent pan endoscopy, biopsies of the tonsil, nasopharynx, or suspected lesions, and received computed tomography (CT) and positron emission

Article History:

Received October 13, 2020

Revised November 1, 2020

Accepted November 2, 2020

Corresponding Author:

Dong Hoon Lee

Department of Otolaryngology-Head and Neck Surgery, Chonnam National University Medical School and Hwasun Hospital, 322 Seoyang-ro, Hwasun-eup, Hwasun 58128, Korea

Tel: +82-61-379-8190

Fax: +82-61-379-7761

E-mail: Leen3L@hanmail.net

TABLE 1. Clinical findings of six patients with head and neck squamous cell carcinoma of unknown primary (HNSCCUP)

Age/sex	Site	Sx duration (mo)	Smoking (pack-years)	Alcohol	Neck level	HPV	EBV	Margin	ECS	PNI	LVI	Grade	Status	FU (mo)
52/M	R	8	8.5	Y	II	ND	Y	N	Y	N	N	MD	NED	91
57/M*	L	3	N	Y	II	ND	ND	N	ND	ND	ND	ND	NED	90
64/M	L	1	N	N	II,III	N	N	N	N	N	N	MD	NED	61
73/M [†]	L	7	25	N	I	ND	ND	N	Y	N	N	WD	NED	67
59/M	R	0.3	25	Y	II	Y	N	N	N	N	N	WD	NED	45
58/M	L	10	45	Y	I,II,III	ND	ND	N	Y	N	Y	WD	NED	39

mo: months, HPV: Human papilloma virus, EBV: Epstein-Barr virus, ECS: extracapsular spread, PNI: perineural invasion, LVI: lymphovascular invasion, FU: follow-up, M: male, R: right, L: left, Y: yes, ND: not described, N: no, MD: moderately-differentiated, WD: well-differentiated, NED: no evidence of disease.

*This patient was treated the lung cancer.

[†]This patient had no recurrence of HNSCCUP, but died of colon cancer at 58 months postoperatively.

tomography computed tomography (PET CT), for exclusion of primary origin site of carcinoma.

Clinical data from the six patients with HNSCCUP were analyzed, including age, sex, smoking, alcohol consumption, symptoms, duration of symptoms, tumor location, neck lymph node status, histopathologic factors (Human papilloma virus [HPV], Epstein-Barr virus [EBV], differentiated grade, resection margin [a positive resection margin was defined as <5 mm], extracapsular spread [ECS], perineural invasion [PNI], lymphovascular invasion [LVI]), postoperative adjuvant therapy, complications, recurrence, and follow-up results.

We performed radical neck dissections involving level I-V, bilateral tonsillectomy, and diagnostic esophagoscopy. All patients underwent RT, with or without concurrent chemotherapy. A Fisher's exact test was used to determine the association between two categorical variables. SPSS version 20.0 was used for all statistical analyses. Statistical significance was considered at $p < 0.05$.

RESULTS

Clinical findings of HNSCCUP are summarized in Table 1. All six patients were males. Their mean age was 58.5 ± 0.5 (range, 52-73 years). All patients presented with masses in the neck. Duration of the symptoms was 4.9 ± 3.7 months (range, 0.3-10 months). Regarding location, HNSCCUP was in the right side for two cases, and the left side for four cases. There were four people that drank and smoked, and three people who did both. The period of pack-years ranged from 8.5-45 with mean period of 25.9 ± 12.9 .

All patients underwent radical neck dissection involving level I-V, bilateral tonsillectomy, and diagnostic esophagoscopy, and postoperative RT with or without concurrent chemotherapy. Histopathologic examination revealed no primary site, other than metastatic cervical squamous cell carcinoma. The most common site was level II ($n=5$, 83.3%), followed by level I ($n=2$, 33.3%) and III ($n=2$, 33.3%). The number of metastatic lymph nodes 2.8 ± 2.5 (range, 1-8).

Differentiated grade was moderately-differentiated in three patients and well-differentiated in two. In the HPV and EBV tests, one patient was positive, for each. Occurrence of ECS, PNI, and LVI were 60.0% (3/5), 0% (0/5), and 20.0% (1/5). The dose of postoperative RT was 5.2 ± 0.5 Gy (range, 4.3-5.6 Gy). Five patients underwent concurrent chemotherapy with RT, only one patient received RT only.

There were no major complications resulting from the surgical interventions. Duration of follow-up was 65.5 ± 20.0 months (range, 39-91 months). There was no recurrence or late detection of primary site of HNSCCUP. All patients with HNSCCUP except one were alive at the time of last follow-up. One patient had no recurrence of HNSCCUP, but died of colon cancer at 58 months postoperatively. Another patient developed lung cancer five years after surgery, but was cured after chemotherapy and RT, and was followed up at the outpatient clinic.

DISCUSSION

HNSCCUP is the presence of a cervical metastatic lymph node, whose primary site cannot be identified despite various examinations.¹⁻³ There are several explanations for HNSCCUP.^{4,7} When small primary carcinomas may be hidden in particular areas, such as the tonsils or the tongue base, it is difficult to identify with physical and radiological examinations due to anatomical complexity of the region, and intrinsic limitations of diagnostic techniques. Recently, it has been suggested that the majority of head and neck carcinoma of unknown primary likely originate from the oropharynx, particularly the palatine tonsil or tongue base.^{6,8,9}

Diagnostic methods for HNSCCUP vary between centers.^{1-5,10,11} Recent advances in immunohistochemistry, molecular markers, endoscopy techniques, imaging and diagnostic methods provide high detection rates of the primary site of HNSCCUP.^{5,10} In most cases, initial the diagnostic workup for HNSCCUP includes history-taking and physical examinations of head and neck regions, specifically tongue base, tonsils, nasopharynx, and pyriform si-

nus, followed by conventional radiological examinations such as ultrasonography, CT, magnetic resonance imaging (MRI), and PET CT.^{1-5,10,11,12} When the primary site is not determined by physical examinations and CT or MRI imaging, PET CT is the next investigation of choice.^{2,10,13} In meta-analysis, PET CT was found to have high sensitivity (97%) and low specificity (68%) in the detection of primary tumors in patients with head and neck carcinoma of unknown primary.¹⁴ We also performed PET CT in all our patients.

Development of molecular markers enable identification of the primary site.^{2,5,6,10,11} The primary site of HPV-positive HNSCCUP is mostly localized in the oropharynx.^{10,15} EBV is associated with nasopharyngeal carcinoma.¹⁰ However, in this study, HPV and EBV were positive in one case each, but it was not helpful in finding the primary site.

In addition, some authors suggested using endoscopy with narrow band imaging to detect the primary site.^{10,16} Narrow band imaging is a new biological endoscopy technique that uses specific light wave lengths, to enhance contrast and microvascular patterns between normal mucosa and malignant lesions in the oral cavity, pharynx, and larynx.^{10,16}

Treatment methods for HNSCCUP include surgery with postoperative RT, and RT with or without chemotherapy, followed by surgery.¹⁻⁶ At our institution, the preferred treatment of HNSCCUP is surgery, including radical neck dissection involving level I-V, bilateral tonsillectomy, and diagnostic esophagoscopy and postoperative RT with concurrent chemotherapy. In a meta-analysis, there was no significant survival difference between patients that received surgery followed by RT, with or without chemotherapy when compared to those that received non-surgical modalities alone.^{2,6} By performing surgery before receiving RT, it is possible to reduce side effects on tissues such as skin and blood vessels, that may occur by performing surgery after RT.² We performed postoperative RT at the neck and possible primary sites, including the nasopharynx, oropharynx, larynx, and hypopharynx.²⁻⁶ In addition, intensive modulated radiation therapy (IMRT) was performed, to reduce RT related toxicity.^{1,2,5,12} In most cases, chemotherapy was administered at the same time as RT, to improve loco-regional control and survival rate, as well as reduce recurrence.^{2,17,18}

Overall five-year survival rate for head and neck carcinoma of unknown primary was 55%.¹ The prognosis was better when the primary site was not identified.¹

In this study, there was no recurrence or late detection of primary site of HNSCCUP, when we performed surgery followed by RT with chemotherapy. Due to the small number of cases, additional studies with more patients will be needed to validate that this method may be effective. In our study, two among six patients with HNSCCUP developed another carcinoma in other organs. So, in these patients, it is recognized that other carcinomas are likely to occur in other organs, and periodic and systemic examinations are

needed.

In conclusion, we have successfully treated patients with HNSCCUP by performing radical neck dissection, bilateral tonsillectomy, and diagnostic esophagoscopy and postoperative RT with concurrent chemotherapy, and recommend using this method as the main treatment method.

ACKNOWLEDGEMENTS

This study was supported by a grant (HCRI 17910-1) from Chonnam National University Hwasun Hospital Institute for Biomedical Science.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Farnebo L, Laurell G, Mäkitie A. A Nordic survey on the management of head and neck CUP. *Acta Otolaryngol* 2016;136:1159-63.
2. Mackenzie K, Watson M, Jankowska P, Bhide S, Simo R. Investigation and management of the unknown primary with metastatic neck disease: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;130(S2):S170-5.
3. Mani N, George MM, Nash L, Anwar B, Homer JJ. Role of 18-Fluorodeoxyglucose positron emission tomography-computed tomography and subsequent panendoscopy in head and neck squamous cell carcinoma of unknown primary. *Laryngoscope* 2016; 126:1354-8.
4. Cianchetti M, Mancuso AA, Amdur RJ, Werning JW, Kirwan J, Morris CG, et al. Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. *Laryngoscope* 2009;119:2348-54.
5. Lanzer M, Bachna-Rotter S, Graupp M, Bredell M, Rücker M, Huber G, et al. Unknown primary of the head and neck: a long-term follow-up. *J Craniomaxillofac Surg* 2015;43:574-9.
6. Dixon PR, Au M, Hosni A, Perez-Ordóñez B, Weinreb I, Xu W, et al. Impact of p16 expression, nodal status, and smoking on oncologic outcomes of patients with head and neck unknown primary squamous cell carcinoma. *Head Neck* 2016;38:1347-53.
7. van de Wouw AJ, Jansen RL, Speel EJ, Hillen HF. The unknown biology of the unknown primary tumour: a literature review. *Ann Oncol* 2003;14:191-6.
8. Nagel TH, Hinni ML, Hayden RE, Lott DG. Transoral laser microsurgery for the unknown primary: role for lingual tonsillectomy. *Head Neck* 2014;36:942-6.
9. Graboyes EM, Sinha P, Thorstad WL, Rich JT, Haughey BH. Management of human papillomavirus-related unknown primaries of the head and neck with a transoral surgical approach. *Head Neck* 2015;37:1603-11.
10. Koivunen P, Bäck L, Laranje J, Irjala H. Unknown primary: diagnostic issues in the biological endoscopy and positron emission tomography scan era. *Curr Opin Otolaryngol Head Neck Surg* 2015; 23:121-6.
11. Jensen DH, Hedback N, Specht L, Høgdall E, Andersen E, Therkildsen MH, et al. Human papillomavirus in head and neck

- squamous cell carcinoma of unknown primary is a common event and a strong predictor of survival. *PLoS One* 2014;9:e110456.
12. Davis KS, Byrd JK, Mehta V, Chiosea SI, Kim S, Ferris RL, et al. Occult primary head and neck squamous cell carcinoma: utility of discovering primary lesions. *Otolaryngol Head Neck Surg* 2014;151:272-8.
 13. Roh JL, Kim JS, Lee JH, Cho KJ, Choi SH, Nam SY, et al. Utility of combined (18)F-fluorodeoxyglucose-positron emission tomography and computed tomography in patients with cervical metastases from unknown primary tumors. *Oral Oncol* 2009;45:218-24.
 14. Zhu L, Wang N. 18F-fluorodeoxyglucose positron emission tomography-computed tomography as a diagnostic tool in patients with cervical nodal metastases of unknown primary site: a meta-analysis. *Surg Oncol* 2013;22:190-4.
 15. Yasui T, Morii E, Yamamoto Y, Yoshii T, Takenaka Y, Nakahara S, et al. Human papillomavirus and cystic node metastasis in oropharyngeal cancer and cancer of unknown primary origin. *PLoS One* 2014;9:e95364.
 16. Piazza C, D Bon F, Peretti G, Nicolai P. 'Biologic endoscopy': optimization of upper aerodigestive tract cancer evaluation. *Curr Opin Otolaryngol Head Neck Surg* 2011;19:67-76.
 17. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al.; Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004;350:1937-44.
 18. Bernier J, Dommene C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al.; European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350:1945-52.