J Med Sci 2020;40(5):215-223 DOI: 10.4103/jmedsci.jmedsci_241_19

ORIGINAL ARTICLE



Head and Neck Lymphomas: Review of 151 Cases

Chao-Yin Kuo¹, Cheng-Ping Shih¹, Li-Hsiang Cheng¹, Shao-Cheng Liu¹, Feng-Hsiang Chiu¹, Yuan-Yung Lin¹, Je-Ming Hu^{2,3,4}, Yueng-Hsiang Chu¹

¹Department of Otolaryngology–Head and Neck Surgery, National Defense Medical Center, Tri-Service General Hospital, ²Department of Surgery, Division of Colorectal Surgery, Tri-Service General Hospital, National Defense Medical Center, ³National Defense Medical Center, Graduate Institute of Medical Sciences, ⁴National Defense Medical Center, School of Medicine, Taipei, Taiwan, Republic of China

Aim: Treatment of lymphoma differs from head and neck carcinomas. The aim of this study was to provide a comprehensive of review lymphomas arising in head and neck region. **Methods:** Patients between 2003 and 2015 with lymphomas in head and neck region were retrospectively reviewed with pathology subtype, age, gender, location, and diagnostic procedure. **Results:** One hundred and fifty-one lymphoma patients were enrolled. Diffuse large B-cell lymphoma accounted for 56.3% of all patients, followed by follicular lymphoma (6.0%) and NK/T-cell lymphoma (6.0%). Nearly 38.4% of patients manifested as enlarged cervical node while another 61.6% presented as extranodal lymphoma with tonsils (21.8%) the most commonly affected site, followed by parotid gland and tongue base. Open surgery or excisional biopsy had the highest sensitivity of 95.8% for a confirmed diagnosis, followed by punch biopsy (74.7%), core biopsy (51.0%), and fine-needle aspiration (2.2%). **Conclusions:** Lymphoma is frequently encountered in head and neck region. Early diagnosis was made possible by detailed examinations and adequate diagnostic procedure with consideration of both procedure sensitivity and risks.

Key words: Lymphoma, hematolymphoid malignancies, head and neck, anatomic distribution, histopathology

INTRODUCTION

Lymphomas represent about 5% of malignancies¹ and up to 15% of all head and neck malignancies.² Lymphomas are divided into Hodgkin's lymphoma (HL) and non-HL (NHL), with the latter further classified into B-cell and T-cell lymphomas. B-cell and T-cell lymphomas have several immunological subtypes which show geographic variation, suggesting its genetic and etiological heterogeneity.³ It can arise in lymph nodes or extranodal lymphoid tissue. The head and neck region is one of the most common sites of extranodal presentation, second after the gastrointestinal tract.⁴ It is necessary to tell lymphomas from other head and neck cancers for their different treatment strategies. The aim of this study is to provide a comprehensive review of head and neck lymphomas.

Received: December 23, 2019; Revised: December 24, 2019; Accepted: January 02, 2020; Published: February 21, 2020 Corresponding Author: Dr. Yueng-Hsiang Chu, Department of Otolaryngology—Head and Neck Surgery, National Defense Medical Center, Tri-Service General Hospital, 325, Section 2, Cheng-Kung Road, Taipei 11490, Taiwan, China. Tel: 886-2-87927192; Fax: 886-2-87927193. E-mail: chuyuenghsiang@gmail.com

METHODS

Patients with malignancies arising in head and neck region, including malignancies in the oral cavity, oropharynx, nasopharynx (NP), hypopharynx, larynx, nasal cavity, paranasal sinuses, thyroid gland, salivary glands, and visceral cancers with neck metastasis were analyzed at the Department of Otolaryngology-Head and Neck Surgery of a tertiary referral hospital from January 2003 to March 2015. Patients with previous diagnosis of lymphoma were excluded from the study. Patients with head and neck lymphoma were retrospectively reviewed for age, gender, histopathology, anatomic location, presence of cervical lymph node involvement, and diagnostic procedures used to achieve diagnosis. Nodal lymphoma (NL) is defined as lymphomas that arise from neck lymph node. Extranodal

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Kuo CY, Shih CP, Cheng LH, Liu SC, Chiu FH, Lin YY, *et al.* Head and neck lymphomas: Review of 151 cases. J Med Sci 2020;40:215-23.

lymphoma (ExNL) is defined as lymphoma arising from tissue other than lymph nodes. Patients presenting both extranodal and nodal involvements were categorized as ExNL. For the diagnosis of lymphoma, open biopsy of neck mass, paranasal sinuses, excision of the submandibular gland, parotidectomy, and tonsillectomy were performed. Fine-needle aspiration (FNA) and core biopsy (CB) may be performed on patients with neck and/or parotid masses. Punch biopsies with nasal cutting forceps (3 mm, Nagashima, Japan) were performed on patients who presented with masses over the oral cavity, oropharynx, NP, or nasal cavity. Formaldehyde-fixed paraffin-embedded tissue sections were treated by immunophenotyping of cell surface antigens as follows: CD3, CD4, CD5, CD8, CD10, CD15, CD20, CD21, CD23, CD30, CD45RO, CD56, CD68, CD79a, kappa and lambda light chain, CyclinD1, Bcl-2, Bcl-6, Ki-67, EMA, AE1/AE3, LMP-1, ALK, MPO, and TdT. In situ hybridization to detect the Epstein-Barr virus-encoding RNA in neoplastic cells and molecular diagnostic examinations for monoclonality were performed when needed. Histopathological examinations of these tissue sections were reviewed by two pathologists from the department of pathology. The classification of hematolymphoid malignancies was made according to the World Health Organization's Classification of Tumors of the Hematopoietic and Lymphoid Tissues (4th Edition, 2008). All abbreviations of lymphoma subtypes in this paper are listed in Table 1. This study was approved by the Institutional Review Board (2-104-05-079).

RESULTS

General data

Total of 1,702 patients had malignancies in head and neck region, among them, 151 (8.9%) patients were diagnosed as lymphomas and enrolled in our study. There were 86 male and 65 female (M/F = 1.3:1) with mean age of 60.3 years (range

Table 1: Abbreviations of subtypes of lymphoma

	<u> </u>
Abbreviation	Explanation
AITL	Angioimmunoblastic lymphoma
ALCL	Anaplastic large cell lymphoma
Burkitt	Burkitt lymphoma
DLBCL	Diffuse large B-cell lymphoma
FL	Follicular lymphoma
MALT	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
MCL	Mantle cell lymphoma
NKTCL	NK/T-cell lymphoma
PTCL	Peripheral T-cell lymphoma
Other BCL	Other B-cell lymphoma
Other TCL	Other T-cell lymphoma

13–98). Nearly 60% of the patients were diagnosed between the ages of 50 and 80 years. It shows bimodal age distribution with larger peak incidence (21.9%) in the age group of 60–70 years and smaller peak incidence in the age group of 20–30 years [Figure 1]. The mean age was younger for HL (38.8 years) compared with NHL (62.3 years). Over half of the patients (7/13, 53.8%) of HL were diagnosed at the age of 20–30 years with higher M/F ratio (2.3:1).

Of the 151 patients of head and neck lymphomas, 112 (74.2%) patients were B-cell lymphoma, followed by 26 (17.2%) patients of T-cell lymphoma, and 13 (8.6%) patients of HL [Figure 2]. As to the subtypes, diffuse large B-cell lymphoma (DLBCL) accounted for 56.3% of all cases, followed by follicular lymphoma (FL) (6.0%), NK/T-cell lymphoma (NKTCL) (6.0%),T-cell lymphoma (PTCL) (5.3%), mixed cellularity HL(MC-HL) (5.3%),and nodular sclerosis HL (NS-HL) (3.3%). Six patients diagnosed with B-cell lymphoma without specific subtype were categorized as "other" B-cell lymphoma; likewise, two patients diagnosed T-cell lymphoma without specific subtype were categorized as "other" T-cell lymphoma.

Nodal lymphomas

The 151 lymphoma patients were consisted of 58 patients (38.4%) of NL and another 93 patients (61.6%) of ExNL. Among the 58 NL patients, 34 (58.6%) were B-cell lymphoma, followed by 13 HL (22.4%), and 11 T-cell lymphoma (19.0%). As to the subtypes [Figure 3], DLBCL accounted for 41.4% of all NL, followed by MC-HL (13.8%), NS-HL (8.6%).

Extranodal lymphomas

Among the 93 ExNL patients, 84% were B-cell lymphoma, with remaining 16% being T-cell lymphoma. It is noted that no HL exists extranodally in our study. The distribution of ExNL subtypes was shown in Figure 4. DLBCL accounted for 65.6% of all ExNL, followed by NKTCL (9.7%) and FL (6.5%).

In ExNL, the primary sites include tonsils, tongue base, NP, soft palate, paranasal sinuses, nasal cavity, oral cavity, parotid, and submandibular gland. Tonsils were the most commonly affected site (35.5%), followed by parotid gland (18.3%), tongue base (12.9%), NP (12.9%), and nasal cavity (10.8%). The detailed anatomic distribution of ExNL in head and neck region was shown in Figure 5. As a whole, Waldeyer's ring is the most commonly affected site in head and neck region.

Histopathological results according to each anatomical site in extranodal lymphoma

Tables 2 and 3 show anatomic sites and histopathological subtypes of ExNL in head and neck region. DLBCL is the

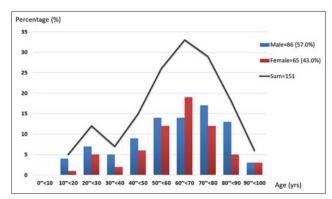


Figure 1: Bimodal age distribution of lymphoma patients in head and neck region

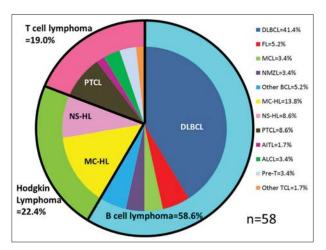


Figure 3: Histopathological distribution of nodal lymphomas in head and neck region (n = 58)

major histopathological subtype in most involved sites, except nasal cavity and soft palate. The nasal cavity was exceptional in histopathological distribution which consisted of 70% of NKTCL and 30% of DLBCL. All NKTCL were extranodal, with majority in the nasal cavity (7/9, 77.8%).

Cases manifested both nodal and extranodal involvement

There were 66 patients with both nodal and extranodal involvement and accounted for 43.7% of all 151 lymphoma patients. Table 4 illustrates the incidence of both nodal and extranodal presentation in ExNLs of head and neck region. NP had the highest incidence (91.7%), followed by the parotid gland (88.2%), tonsils (81.8%), and tongue base (58.3%).

Diagnostic procedures for lymphoma in head and neck region

Confirmation of lymphoma required the following procedures/techniques: FNA and CB of the neck or parotid mass;

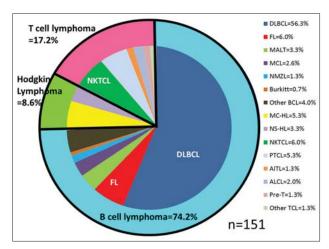


Figure 2: Histopathological distribution of lymphomas in head and neck region (n = 151)

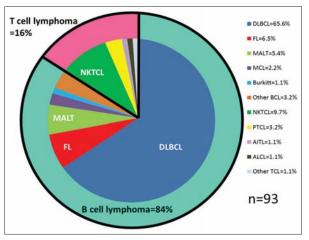


Figure 4: Histopathological distribution of extranodal lymphomas in head and neck region (n = 93)

punch biopsy over lesion in the oral cavity, oropharynx, NP, nasal cavity; open surgeries - including tonsillectomy, excision of neck mass or submandibular gland, and parotidectomy. In the diagnosis of 151 head and neck lymphoma, FNA was performed totally 45 times, CB 51 times, punch biopsy 75 times, and open surgery 71 times. Figure 6 illustrates the sensitivity of different diagnostic procedures. For 71 times of open surgeries - two were negative, one was suspected malignancy/lymphoma, and sixty-eight were positive for lymphoma; the sensitivity is 95.8%. For 75 times of punch biopsies, the number of negative, suspected malignancy/lymphoma, and positive were 15, 4, and 56, respectively; the sensitivity was 74.7%. For 51 times CB procedures, the number of negative, atypia, suspected malignancy/lymphoma, and positive were 9, 14, 2, and 26, respectively; the sensitivity

Table 2: Anatomic sites-oriented extranodal lymphomas of head and neck region (n=93)

Site	Histopathology	Percentage
Tonsil (<i>n</i> =33; 35.5%)	DLBCL (n=26)	78.8
	FL (<i>n</i> =2)	6.1
	MCL (<i>n</i> =1)	3.0
	NKTCL (n=1)	3.0
	Burkitt (n=1)	3.0
	ALCL (n=1)	3.0
	Other BCL (n=1)	3.0
Parotid gland (<i>n</i> =17; 18.3%)	DLBCL (n=11)	64.7
	PTCL (n=3)	17.6
	FL (<i>n</i> =2)	11.8
	Other BCL (n=1)	5.9
Tongue base (n=12; 12.9%)	DLBCL (n=11)	91.7
	FL (<i>n</i> =1)	8.3
Nasopharynx (n=12; 12.9%)	DLBCL (n=5)	41.7
	MALT (<i>n</i> =3)	25.0
	FL (<i>n</i> =1)	8.3
	AITL (n=1)	8.3
	NKTCL (n=1)	8.3
	Other BCL	8.3
Nasal cavity (n=10; 10.8%)	NKTCL (n=7)	70.0
	DLBCL (n=3)	30.0
Oral cavity (<i>n</i> =3; 3.2%)	DLBCL (n=2)	66.7
	MALT (n=1)	33.3
Soft palate (<i>n</i> =2; 2.2%)	MCL (<i>n</i> =1)	50.0
	Other TCL (<i>n</i> =1)	50.0
Paranasal sinuses (n=2; 2.2%)	DLBCL (n=2)	100.0
Submandibular gland (n=2; 2.2%)	DLBCL (n=1)	50.0
	MALT $(n=1)$	50.0

is 51.0%. For 45 times of FNA, the number of negative, atypia, suspected malignancy/lymphoma, and positive were 15, 19, 10, and 1, respectively; the sensitivity is 2.2% only. Open surgeries have the highest sensitivity or true positive rate of 95.8%, followed by punch biopsy (74.7%), CB (51.0%), and FNA (2.2%). The sensitivity of each diagnostic procedure is statically different (ANOVA, P < 0.00001).

For 58 NL, 39 patients were diagnosed by excision of the neck node and 19 patients by CB. For 93 ExNL, 56 patients were diagnosed by punch biopsy, 29 patients by open surgery, 7 patients by CB of cervical lymph node, and 1 patient by FNA of parotid tumor. The procedures for confirmed diagnosis of ExNL are shown in Table 5. Punch biopsies were widely performed on extranodal sites except

Table 3: Histopathology-oriented of extranodal lymphomas of head and neck region (n=93)

Histopathology	Site	Percentage	
DLBCL (n=61)	Tonsil (n=26)	42.6	
	Tongue base (n=11)	18.0	
	Parotid gland (n=11)	18.0	
	Nasopharynx (n=5)	8.2	
	Nasal cavity (n=3)	4.9	
	Paranasal sinuses (n=2)	3.3	
	Oral cavity (n=2)	3.3	
	Submandibular gland (n=1)	1.6	
FL (<i>n</i> =6)	Tonsil (<i>n</i> =2)	33.3	
	Parotid gland (n=2)	33.3	
	Tongue base (n=1)	16.7	
	Nasopharynx (n=1)	16.7	
MALT (n=5)	Nasopharynx (n=3)	60.0	
	Oral cavity (n=1)	20.0	
	Submandibular gland (n=1)	20.0	
MCL (<i>n</i> =2)	Tonsil (<i>n</i> =1)	50.0	
	Soft palate (n=1)	50.0	
Burkitt (n=1)	Tonsil (<i>n</i> =1)	100.0	
PTCL (<i>n</i> =3)	Parotid gland (n=3)	100.0	
NKTCL (n=9)	Nasal cavity (n=7)	77.8	
	Nasopharynx (n=1)	11.1	
	Tonsil (<i>n</i> =1)	11.1	
AITL (n=1)	Nasopharynx (n=1)	100.0	
ALCL (n=1)	Tonsil (<i>n</i> =1)	100.0	

parotid and submandibular gland. Tonsil lymphomas were either diagnosed by punch biopsy (60.6%) or by standard tonsillectomy (27.3%). For the salivary gland, most patients received open surgery included parotidectomy or excision of submandibular gland under the initial impression of primary salivary gland neoplasm. Among 66 patients with both nodal and extranodal involvement, seven of them had diagnosed by CB of cervical lymph node and another ten patients confirmed by excisional biopsy of cervical lymph node.

DISCUSSION

Lymphomas represent 5%–15% of all malignant neoplasms in head and neck region.^{2,5,6} The incidence in our study was 8.9%. It is well known that the incidence of lymphoma has been increasing in recent years. Possible causes include increasing elderly population, more prevalent organ transplantation, and improved AIDS survival rate.⁷ Our study showed male patients

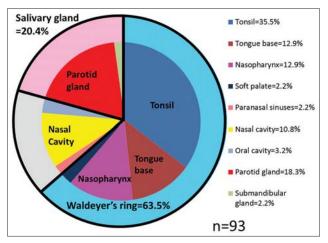


Figure 5: Anatomic distribution of extranodal lymphoma in head and neck region (n = 93). Waldeyer's ring includes tonsils, tongue base, soft palate, and nasopharynx. Salivary gland includes parotid gland and submandibular gland

Table 4: Incidence of both nodal and extranodal presentation in extranodal lymphoma of head and neck region

	1			
Anatomic site-oriented (n=93)	Patient (%)	Histopathology-oriented (<i>n</i> =89*)	Patient (%)	
Tonsil	27/33 (81.8)	DLBCL	44/61 (72.1)	
Tongue base	7/12 (58.3)	FL	6/6 (100.0)	
Nasopharynx	11/12 (91.7)	MALT	2/5 (40.0)	
Soft palate	1/2 (50.0)	MCL	1/2 (50.0)	
Paranasal sinuses	1/2 (50.0)	Burkitt	1/1 (100.0)	
Nasal cavity	3/10 (30.0)	PTCL	3/3 (100.0)	
Oral cavity	0/3 (0)	NKTCL	3/9 (33.3)	
Parotid gland	15/17 (88.2)	AITL	1/1 (100.0)	
Submandibular gland	1/2 (50.0)	ALCL	1/1 (100.0)	

All abbreviations of lymphoma subtypes in this paper are listed in Table 1. *3 cases categorized as other B-cell lymphoma and 1 case categorized as other T-cell lymphoma had both nodal and extranodal involvement are listed on the anatomic site-oriented analysis but not in the histopathology-oriented analysis)

were slightly more predominant, with male to female ratio of 1.3:1 in all lymphoma patients and even higher ratio of 2.3:1 in HL, which is compatible with previous literature.^{1,2}

HL comprises approximately 11% of lymphoma in the US,⁶ 13% in China,⁸ and 5% in Japan,^{3,9} while we reported incidence of 8.6%. Nakatsuka and Aozasa¹⁰ have previously highlighted that bimodal age distribution in HL resulting from MC-HL occurring in the elderly and NS-HL occurring in younger age groups. Similarly, all patients aged above 70 years with HL were MC-HL patients in our study. HL rarely presents as an extranodal disease^{2,4,11} and the ExNL were exclusively made up of NHL in our study. On the other hand, 67.4% (93 of 138 cases) of NHL manifested extranodal involvement in our study, which is similar to the previous study in Japan,²

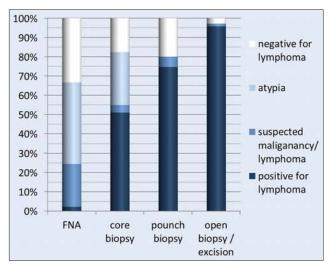


Figure 6: Histopathologic results of diagnostic procedures in lymphoma of head and neck region. FNA = Fine-needle aspiration. Negative for lymphoma included free of malignancy, inadequate sampling and non-diagnostic results. Open surgery include tonsillectomy, excision of neck mass, submandibular gland, parotidectomy

but higher than most reports from Western countries. ^{12,13} Yang *et al.*⁸ reported that the incidence of extranodal NHL varies geographically, with higher incidence in Asia³. It might because of higher incidence of NKTCL in Asian patients, which mainly presents as an extranodal disease. ¹⁴

The mean age of B-cell and T-cell lymphoma patients was 63.7 and 56.6 years, respectively. The trend shows higher prevalence of T-cell lymphoma in younger people is similar to another study in Taiwan.⁴ The ratio of B-cell to T-cell lymphoma has been reported to be 2.6–3.9 in all lymphomas^{3,9,15} and 4.1–7.4 in lymphomas of head and neck region.^{2,11,16} B-cell to T-cell ratio is even higher in ExNL in head and neck region, which has been reported as up to 7.6 in previous literature.^{2,17} In our study, the ratio of B-cell to T-cell lymphoma of all cases enrolled and ExNL were 4.3 and 5.2, respectively.

In our study of ExNL in head and neck region, DLBCL was the most common type, followed by NKTCL and FL. This result agreed with previous studies^{2,3,18} and seemed universal. T-cell lymphoma showed geographic differences.^{14,19} In our study, NKTCL was the most common type of T-cell lymphoma and occurred exclusively as extranodal disease (9.7% of ExNL), followed by PTCL. This result was compatible with other similar studies from China and Taiwan.^{4,20} A study on head and neck lymphoma in Japan showed higher rate of PTCL than NKTCL,² which is in accordance with previous data reporting that NKTCL is more frequent in other Asian countries but Japan.¹⁹

The Waldeyer's ring comprises of network of lymphoid tissue over the palatine tonsils, NP, tongue base, and soft palate. It is the most common site of ExNL in head and neck region and

Table 5: Diagnostic procedures for extranodal lymphoma in head and neck region

	Punch biopsy	FNA	Core biopsy	Open surgery [†]		
Tonsil	20		2*			
Tongue base	12					
Nasopharynx	8		2*	2*		
Soft palate	2					
Paranasal sinuses	1			1		
Nasal cavity	10					
Oral cavity	3					
Parotid gland		1	3*	13(7+6*)		
Submandibular gland				2		
Total (patients)	56	1	7	29		

FNA=Fine needle aspiration. *Diagnosis made by cervical lymph node biopsy. †Open surgery include excisional biopsy of neck mass, submandibular gland, parotidectomy and tonsillectomy, described as follows: Tonsil: 9 cases of tonsillectomies and 2 of excisional biopsy of neck masses; Nasopharynx: 2 cases of excisional biopsy of neck masses; Paranasal sinus: one case of lateral rhinotomy; Parotid gland: 7 cases of parotidectomy and 6 of excisional biopsy of neck mass; Submandibular gland: 2 cases of excision of submandibular gland

accounts for 32%–74% of ExNL.^{2,4,12,17,18,21} Our study found Waldeyer's ring made up 63.5% of ExNL cases in head and neck region, with tonsils being the most commonly involved tissue. DLBCL was the most common histopathological type found in Waldeyer's ring, which constituted about 50%–60% of all ExNL in Waldeyer's ring.^{2,11,12,18,20,22} The incidence of DLBCL was even higher in the tongue base, estimated to be 91.7%, as shown in Table 2. NP has different distribution of histopathological types compared to other sites of Waldeyer's ring, with lower incidence of DLBCL, but higher NKTCL and Mucosa-Associated Lymphoid Tissue (MALT).²²

The second most common site of ExNL after tonsils was the parotid gland (18.3%), which is in agreement in previous literatures. 12,18,20 Together with submandibular gland, major salivary gland accounted for 20.4% of ExNL in head and neck region. Histopathologically, major salivary gland lymphoma was mainly composed of MALT, FL, DLBCL, and PTCL.^{2,11,18,20} MALT typically arises in the parenchyma, which is believed to be associated with Sjogren's syndrome, whereas FL often arises in the intraparotid lymph node. In our study, DLBCL was comprised 63.2% of salivary lymphoma, which is higher than in previous literature suggested (13.3 and 30.8%). 18,20 FL, MALT, and PTCL constituted 10.5%, 15.8%, and 5.3%, respectively. A study on MALT of head and neck region collected 36 cases and found 20 cases occurred in the ocular adnexa and 14 in parotid gland.²³ However, we found no MALT in parotid gland and only 1 of 5 MALT cases occurred in the submandibular gland.

Lymphomas of the nasal cavity constituted 10.8% of ExNL in our study. The incidence ratio of nasal cavity ExNL was reported to be 28.4% in China, 10.6% in Japan, and very rare in Western countries. 2,12,18,20 These nasal lymphomas are predominantly NKTCL.11 In our study, NKTCL was composed of 70% nasal cavity ExNL, with the remaining 30% being DLBCL. Wang et al.20 reported 29 cases of nasal cavity ExNL showed similar results of 65.6% of NKTCL and 20.7% of DLBCL. Lymphoma is the second most common malignancy of paranasal sinuses. DLBCL is the most common type ²⁴ [Table 2]. In the US, the oral cavity constitutes 2% of ExNL and often affects the palate, gingiva, and tongue.¹¹ Histopathologically, oral cavity lymphoma is mainly comprised of DLBCL, followed by FL and MALT.¹¹ We found three cases (3.2%) of oral cavity ExNL (palate, buccae, and tongue). Two were DLBCL and one was MALT.

The definition of ExNL is controversial, especially in patients with both nodal and extranodal involvement. Krol et al.25 proposed that the definition of extranodal NHL should include disseminated diseases, as long as the extranodal site is clinically dominant. Since our study focused on initial diagnostic approach, we defined ExNL as patients clinically presenting an extranodal disease with or without lymph node involvement. Therefore, ExNL patients may receive diagnostic procedures over either extranodal sites or cervical lymph nodes. We presented the incidence of both nodal and extranodal involvement in ExNL of head and neck region by primary extranodal site and histopathological types [Table 4]. In histopathology-orientated analysis, NKTCL showed the lowest incidence (33.3%, 3/9) of both nodal and extranodal involvement while FL the highest (100%, 6/6). Yang et al.8 showed similar results with NKTCL the lowest nodal to extranodal ratio and FL the highest. In anatomic site-oriented analysis, NP had the highest incidence (91.7%) of both extranodal and nodal involvement, followed by the parotid gland (88.2%) and tonsils (81.8%).

The excisional biopsy of lymph nodes is traditionally considered the standard diagnostic procedure for NL. With advanced biopsy devices, radiologically guided techniques, immunohistochemistry and flow cytometry, many authors advocate for less invasive techniques with considerable diagnostic value.²⁶⁻²⁸ Hay *et al.*²⁸ reported FNA cytology combined with immunohistochemistry/flow cytometry can reach sensitivity and positive predictive value of more than 95%. However, FNA often results in inadequate tissue sampling and is unable to provide microscopic architecture. Consequently, many authors suggest that ultrasound-guided CB may be superior to FNA and may replace open biopsy.^{26,29-31} Regarding the diagnosis of all 151 lymphoma patients, we performed punch biopsy, CB,

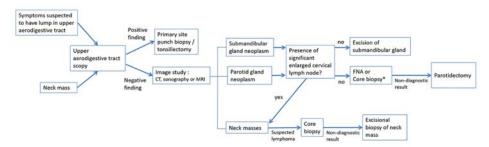


Figure 7: Diagnostic flow chart for head and neck lymphomas.*Concerning potential facial nerve injury, core biopsy are preferred in more superficial part of parotid gland

FNA, and open surgery. As expected, open surgery has the highest sensitivity or true positive rate of 95.8%, followed by punch biopsy (74.7%), CB (51.0%), and FNA (2.2%). In FNA procedure, one-third of results were negative for lymphoma, the false-negative rate too high to accept as a reliable diagnostic procedure for lymphoma. In 58 cases of NL, 39 cases (67.2%) were diagnosed by excisional biopsy of the neck node and 19 cases (32.8%) by CB. Burke et al.27 compared surgical biopsy, CB, and FNA of the neck mass, revealing similar results with no case diagnosed by FNA. Thus, despite advantages in diagnosing head and neck carcinoma with metastatic lymphadenopathy, 32,33 FNA was suboptimal for diagnosing lymphoma. We suggest CB of neck lymph nodes for patients medically unfit for open surgery. In our experience in ExNL diagnosis, punch biopsy is useful for lump lesions located at tonsils, tongue base, NP, soft palate, nasal, and oral cavity. For ExNL of the major salivary glands, most patients received open surgeries such as parotidectomy or excision of submandibular gland. The major complications of CB on parotid gland are facial nerve injury and possible tumor seeding, though facial nerve palsy after CB on the parotid gland is rarely reported in previous literature.34-36 Since 88.2% of ExNLs of parotid gland also involved neck lymph nodes, we can choose excisional biopsy of neck lymph node to abate possible facial nerve injury.

The procedure-related complications also need to be taken into consideration. For example, for patient presented with neck mass and NP mass, performing office-based NP punch biopsy can provide has high diagnostic rate and minimized the risks of neck open surgery as well. By contrast, we had experienced an elderly female patient presented with tonsil mass and an ipsilateral enlarged neck node over left side level IV region which suspected to be lymphoma on MRI. We performed excisional biopsy and confirm the diagnosis of lymphoma. However, chylorrhea developed and thus the chemotherapy was delayed for weeks until the wound healed. Therefore, the sensitivity and the risks of diagnostic procedure, which is potentially conflicting, should be carefully considered.

Figure 7 demonstrates our current diagnostic flow chart for head and neck lymphomas, though we still believed that the diagnostic procedure should be evaluated on an individualized patient and institution basis.

CONCLUSIONS

Our study demonstrated a comprehensive picture of lymphomas in head and neck region that frequently encountered in general clinical practice. Early diagnosis was made possible by detailed examinations and adequate diagnostic procedure with consideration of both procedure sensitivity and risks.

Financial support and sponsorship

No financial support was received for this study.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Cooper JS, Porter K, Mallin K, Hoffman HT, Weber RS, Ang KK, et al. National cancer database report on cancer of the head and neck: 10-year update. Head Neck 2009:31:748-58.
- Iguchi H, Wada T, Matsushita N, Oishi M, Yamane H. Anatomic distribution of hematolymphoid malignancies in the head and neck: 7 years of experience with 122 patients in a single institution. Acta Otolaryngol 2012;132:1224-31.
- 3. Aoki R, Karube K, Sugita Y, Nomura Y, Shimizu K, Kimura Y, *et al.* Distribution of malignant lymphoma in Japan: Analysis of 2260 cases, 2001-2006. Pathol Int 2008;58:174-82.
- 4. Chen SW, Chang ST, Lu CL, Hwang WS, Tsao CJ, Huang WT, *et al.* Upper aerodigestive tract lymphoma in Taiwan. J Clin Pathol 2010;63:888-93.
- 5. Boring CC, Squries TS, Tong T. Cancer statistics, 1993. CA Cancer J Clin 1993;43:7-26.

- Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
- 7. Zapater E, Bagan JV, Carbonell F, Basterra J. Malignant lymphoma of the head and neck. Oral Dis 2010;16:119-28.
- 8. Yang QP, Zhang WY, Yu JB, Zhao S, Xu H, Wang WY, *et al.* Subtype distribution of lymphomas in Southwest China: Analysis of 6,382 cases using WHO classification in a single institution. Diagn Pathol 2011;6:77.
- 9. Miura Y, Fukuhara N, Yamamoto J, Kohata K, Ishizawa K, Ichinohasama R, *et al.* Clinicopathological features of malignant lymphoma in Japan: The Miyagi Study. Tohoku J Exp Med 2011;224:151-60.
- 10. Nakatsuka S, Aozasa K. Epidemiology and pathologic features of Hodgkin lymphoma. Int J Hematol 2006;83:391-7.
- 11. Weber AL, Rahemtullah A, Ferry JA. Hodgkin and non-Hodgkin lymphoma of the head and neck: Clinical, pathologic, and imaging evaluation. Neuroimaging Clin N Am 2003;13:371-92.
- Etemad-Moghadam S, Tirgary F, Keshavarz S, Alaeddini M. Head and neck non-Hodgkin's lymphoma: A 20-year demographic study of 381 cases. Int J Oral Maxillofac Surg 2010;39:869-72.
- 13. Hanna E, Wanamaker J, Adelstein D, Tubbs R, Lavertu P. Extranodal lymphomas of the head and neck. A 20-year experience. Arch Otolaryngol Head Neck Surg 1997;123:1318-23.
- 14. Kwong YL, Anderson BO, Advani R, Kim WS, Levine AM, Lim ST, *et al.* Management of T-cell and natural-killer-cell neoplasms in Asia: Consensus statement from the Asian Oncology Summit 2009. Lancet Oncol 2009;10:1093-101.
- 15. Nakamura S. The World Health Organization classification of malignant lymphomas in Japan: Incidence of recently recognized entities. Pathol Int 2000;50:696-702.
- 16. Walter C, Ziebart T, Sagheb K, Rahimi-Nedjat RK, Manz A, Hess G. Malignant lymphomas in the head and neck region A retrospective, single-center study over 41 years. Int J Med Sci 2015;12:141-5.
- 17. Shima N, Kobashi Y, Tsutsui K, Ogawa K, Maetani S, Nakashima Y, *et al.* Extranodal non-Hodgkin 's lymphoma of the head and neck. Cancer 1990;66:1190-7.
- Hart S, Horsman JM, Radstone CR, Hancock H, Goepel JR, Hancock BW. Localised extranodal lymphoma of the head and neck: The Sheffield Lymphoma Group experience (1971-2000). Clin Oncol (R Coll Radiol) 2004;16:186-92.
- Vose J, Armitage J, Weisenburger D, International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study:

- Pathology findings and clinical outcomes. J Clin Oncol 2008;26:4124-30.
- Wang J, Cai CP, He SF, Wang SL. Characteristics and prognostic factors for head and neck non-Hodgkin's lymphoma in Chinese patients. J Laryngol Otol 2013;127:699-704.
- Batuecas Caletrío A, Gómez González JL, Muñoz Herrera A, Blanco Pérez P, Serradilla López JM, Gil Melcón M, et al. Non Hodgkin's lymphoma in the ENT field. Acta Otorrinolaringol Esp 2005;56:215-8.
- 22. Lee SJ, Suh CW, Lee SI, Kim WS, Lee WS, Kim HJ, et al. Clinical characteristics, pathological distribution, and prognostic factors in non-Hodgkin lymphoma of Waldeyer's ring: Nationwide Korean study. Korean J Intern Med 2014;29:352-60.
- 23. Wenzel C, Fiebiger W, Dieckmann K, Formanek M, Chott A, Raderer M. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue of the head and neck area: High rate of disease recurrence following local therapy. Cancer 2003;97:2236-41.
- 24. Cuadra-Garcia I, Proulx GM, Wu CL, Wang CC, Pilch BZ, Harris NL, et al. Sinonasal lymphoma: A clinicopathologic analysis of 58 cases from the Massachusetts General Hospital. Am J Surg Pathol 1999;23:1356-69.
- 25. Krol AD, le Cessie S, Snijder S, Kluin-Nelemans JC, Kluin PM, Noordijk EM. Primary extranodal non-Hodgkin's lymphoma (NHL): The impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. Ann Oncol 2003;14:131-9.
- Pfeiffer J, Kayser G, Ridder GJ. Sonography-assisted cutting needle biopsy in the head and neck for the diagnosis of lymphoma: Can it replace lymph node extirpation? Laryngoscope 2009;119:689-95.
- 27. Burke C, Thomas R, Inglis C, Baldwin A, Ramesar K, Grace R, *et al.* Ultrasound-guided core biopsy in the diagnosis of lymphoma of the head and neck. A 9 year experience. Br J Radiol 2011;84:727-32.
- 28. Hay A, Pai I, Pitkin L, Williamson P, Wilson P, Deery A. Value of fine needle aspiration cytology in head and neck lymphoma: Experience in a head and neck cancer unit in the United Kingdom. Acta Otolaryngol 2011;131:1226-31.
- Demharter J, Müller P, Wagner T, Schlimok G, Haude K, Bohndorf K. Percutaneous core-needle biopsy of enlarged lymph nodes in the diagnosis and subclassification of malignant lymphomas. Eur Radiol 2001;11:276-83.
- 30. Das DK. Value and limitations of fine-needle aspiration cytology in diagnosis and classification of lymphomas: A review. Diagn Cytopathol 1999;21:240-9.

- 31. Roh JL, Lee YW, Kim JM. Clinical utility of fine-needle aspiration for diagnosis of head and neck lymphoma. Eur J Surg Oncol 2008;34:817-21.
- 32. Schwarz R, Chan NH, MacFarlane JK. Fine needle aspiration cytology in the evaluation of head and neck masses. Am J Surg 1990;159:482-5.
- 33. Gertner R, Podoshin L, Fradis M. Accuracy of fine needle aspiration biopsy in neck masses. Laryngoscope 1984;94:1370-1.
- 34. Buckland JR, Manjaly G, Violaris N, Howlett DC.

- Ultrasound-guided cutting-needle biopsy of the parotid gland. J Laryngol Otol 1999;113:988-92.
- Kesse KW, Manjaly G, Violaris N, Howlett DC. Ultrasound-guided biopsy in the evaluation of focal lesions and diffuse swelling of the parotid gland. Br J Oral Maxillofac Surg 2002;40:384-8.
- 36. Wan YL, Chan SC, Chen YL, Cheung YC, Lui KW, Wong HF, *et al.* Ultrasonography-guided core-needle biopsy of parotid gland masses. AJNR Am J Neuroradiol 2004;25:1608-12.