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Can imaging features be used to predict prognosis in extranodal head and neck lymphomas?

Abstract

Objective: To determine the imaging features of extranodal head and neck lymphoma (EHNL) and their influence on prognosis.

Methods: We retrospectively analyzed the clinical and imaging findings of patients who received a diagnosis of EHNL from January 2010 to September 2018. We documented their demographic characteristics and clinical, biochemical, and imaging features. We evaluated the number, location, size, margin, shape, enhancement degree and pattern, local tumor invasiveness, regional lymph node, and presence of necrosis using computed tomography or magnetic resonance imaging. The influence of imaging features on prognosis was assessed using univariate and multivariate logistic regression analyses.

Results: Sixty-nine patients with EHNL (male/female: 39/30; mean age ± SD: 59.3±17 years; age range: 18-87 years) were included. The most frequent histological type was non-Hodgkin's lymphoma (97.1%) with diffuse large B-cell lymphoma (47.8%) as subtype. Solitary involvement was more frequent (58%). The most commonly involved locations were the Waldeyer's ring (60.9%) and sinonasal region (13%). Univariate analysis revealed that tumor size of 5 cm or larger, ill-defined margin, irregular shape, presence of local invasion, presence of necrosis, and heterogeneous irregular enhancement were more frequent in patients with a poor prognosis ($P < .05$). In contrast, multivariate analysis revealed that all these factors independently had no significant influence on prognosis.

Conclusion: Radiological characteristics of tumor including size, margin, shape, contrast enhancement pattern, local tumor invasiveness, and presence of necrosis impacted prognosis in univariate analysis but not in multivariate analysis. However, further studies are needed to firmly establish the imaging features of EHNL in predicting prognosis.

Keywords: CT, extranodal lymphoma, head, MRI, neck, prognosis

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Introduction

Lymphoma is the third most commonly diagnosed malignancy worldwide, representing 3% of all malignant tumors, and the third most frequent head and neck malignancy after squamous cell carcinoma (46%) and thyroid carcinoma (33%).[1] Extranodal lymphomas are defined as lymphomatous infiltration of nonlymphoid tissues that can originate in almost any organ, with the most common involvement being the gastrointestinal tract, head and neck region, central nervous system, lung, bone, and skin. Extranodal head and neck lymphoma (EHNL) generally manifests as a mass lesion mimicking other infectious or neoplastic diseases.[2,3] The diagnosis of EHNL remains challenging, particularly due to a variety of clinical manifestations. Imaging techniques *contribute* to differential diagnosis and proper management.[4,5] Previous studies have reported the importance of clinical characteristics of EHNL worldwide; however, only few studies have systematically discussed the imaging features of EHNL and influence of these features on prognosis.[4,6,7] The main purpose of this study was to identify the imaging features of EHNL that can help differentiate it from other malignancies and evaluate whether these features could be used as prognostic factors.

Methods

Study Population

Between January 2010 and September 2018, we retrospectively evaluated the medical records and imaging studies of patients with head and neck lymphoma. The inclusion criteria were as follows: (1) presence of EHNL, (2) computed tomography (CT) or/

and magnetic resonance imaging (MRI) scans of the head and neck region, and (3) a definitive histopathologic diagnosis of lymphoma. The exclusion criteria were history of any other type of cancer and contraindications for contrast material, CT, or MRI. All patients had biopsy proven lesions of either primary or secondary EHNL. The medical records were reviewed for demographic characteristics, lymphoma subtypes, presenting symptoms, medical history, biochemical profile [serum lactate dehydrogenase (LDH) and β 2-microglobulin levels], imaging findings, treatment plans, and outcomes. In addition, all tumors were staged according to the Ann Arbor staging system.

Evaluation of Imaging Findings

All patients underwent contrast-enhanced CT or/and MRI examination. CT scans were performed with contrast medium using 64-slice and 128-slice CT scanners (Aquilion 64; Toshiba Medical Systems, Otawara, Japan; Revolution EVO Gen 2; GE Healthcare, Milwaukee, WI, USA). MRI scans were acquired on a 1.5T MRI scanner (Siemens Avanto, Erlangen, Germany) and 3T MRI scanner (GE Healthcare) with intravenous gadolinium contrast administration (Dotarem, gadoterate meglumine/Gd-DOTA; Guerbet, Aulnay-sous-Bois, France). Two experienced radiologists (5 and 7 years of experience) retrospectively analyzed all images on the basis of *consensus but without knowledge of patients' data*.

All lesions were evaluated with respect to the number (solitary/multiple), location, size (*≥5 cm* in *diameter*), margin (well- and ill-defined), shape (regular/irregular), contrast enhancement degree and pattern, local tumor invasiveness, presence of necrosis, calcification or hemorrhage, and regional lymph node involvement on imaging studies. In patients with multiple-site involvement, imaging features of the largest tumor were recorded. Tumor size was defined by unidimensional measurement of the tumor's longest diameter. Contrast enhancement degree was classified as mild (+), moderate (++), and marked (+++) compared to the adjacent muscle tissue. The patterns of contrast enhancement were classified as homogeneous nodular and heterogeneous irregular.

We also performed univariate and multivariate analyses to determine whether imaging data can be used to predict patient's outcome. The patients were *divided into the following two groups: good* outcome group comprising patients who are alive or disease free for more than 2 years and *poor outcome group* comprising exitus patients or those with relapse within 2 years. Univariate analysis was performed to compare the imaging findings of tumors between the two groups. A multiple logistic regression analysis was performed to assess the influence of imaging features on prognosis.

Main points

- Extranodal lymphomas can arise in almost any organ in the head and neck region, with the Waldeyer's ring, sinonasal region, orbit and salivary glands being the most commonly involved regions.
- The rarely involved sites are the submandibular gland, thyroid gland, larynx, muscles, bones, or nerve fibers.
- Extranodal head and neck lymphoma (EHNL) presents with various clinical manifestations depending on size and location.
- Imaging features including tumor size of 5 cm or larger, ill-defined margin, irregular shape, presence of local invasion, presence of necrosis, and heterogeneous irregular enhancement pattern seem to be potential prognostic markers in EHNL.

This retrospective study was approved by our Institutional Review Board (November 27, 2018, IRB number: 25403353-050), and written *informed consent was obtained from all patients included in the study.*

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 24.0 (IBM SPSS Corp.; Armonk, NY, USA) Continuous variables were expressed as median (minimum-maximum) and categorical variables as number (percentage). Continuous variables were tested for normality by using

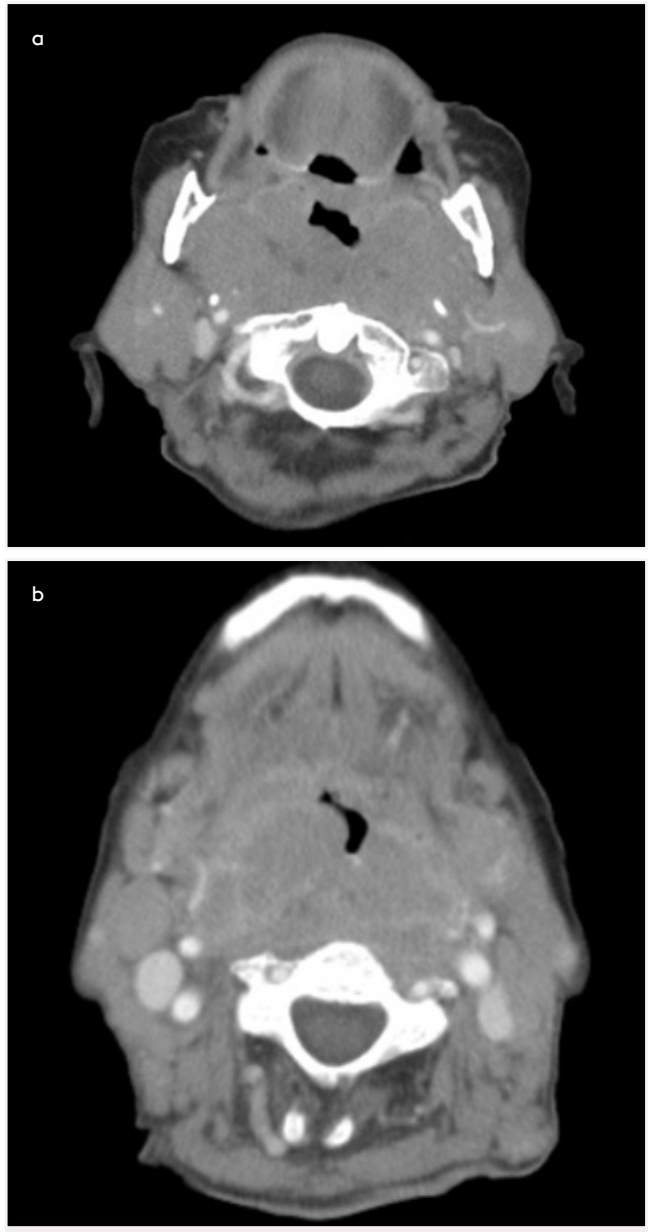

Figure 1. a, b. A 87-year-old female patient with secondary EHNL (NHL, Diffuse large B-cell lymphoma, stage II E) in Waldeyer's ring, received chemotherapy and exitus at 4 months. Axial contast-enhanced CT images (a and b) show ill-defined, irregular shaped, moderately heterogenous enhanced mass affected bilateral tonsils, nasopharynx and base of tongue.

the Shapiro-Wilk test. The associations between categorical variables were determined using Fisher's exact test and Pearson's chi-square tests. The influence of imaging features on prognosis was assessed using univariate and multivariate logistic regression analyses. A $P < .05$ was considered statistically significant.

Results

Patients' Demographics and Clinical Findings

Sixty-nine eligible patients (male/female: 39/30; mean ± SD age: 59±17 years, age range: 18-87 years) were enrolled in this study. Most of the patients (n = 67, 97.1%) had non-Hodgkin's lymphoma (NHL); among which, 33 (47.8%) patients had *diffuse* large B-cell *lymphoma* (Figure 1) and 12 (17.4%) had marginal zone lymphoma. Extranodal involvement in Hodgkin's lymphoma (HL), detected in only 2 (2.9%) patients, was observed in the Waldeyer's ring and subtyped as *nodular sclerosis and lymphocyte-rich* type (Figure 2). The most common presenting symptoms were mass swelling (65.2%) and dyspnea (30.4%). Prognostic B symptoms were observed in only 9 patients (13%). Mean serum LDH and β2-microglobulin levels were 389 (range: 149-2540 IU/L) and 3 (range: 2-7

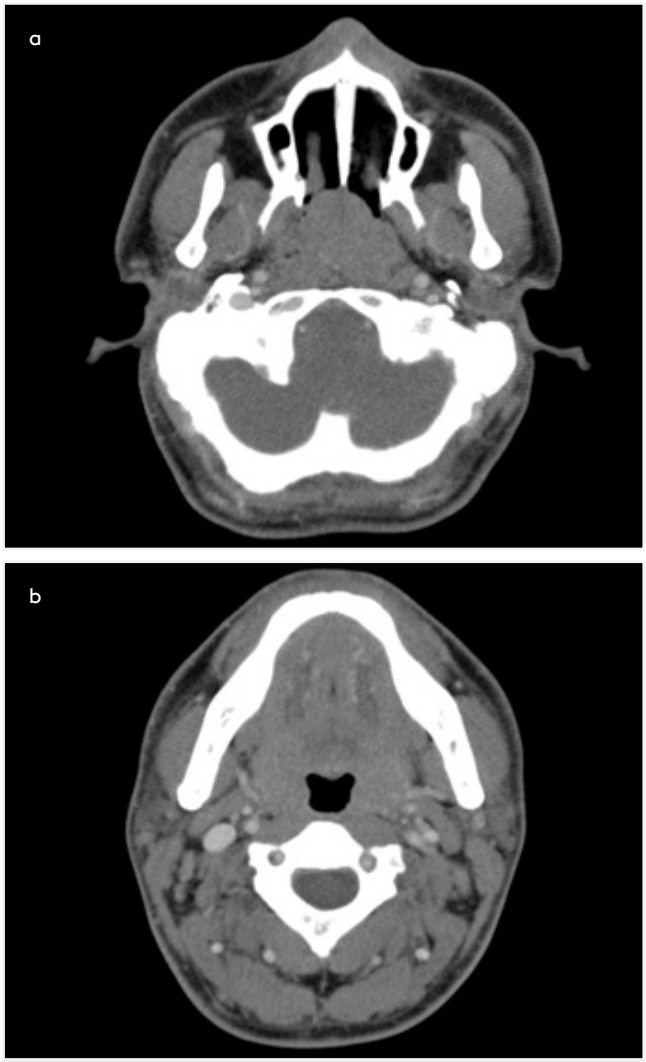

Figure 2. a, b. A 36-year-old male patient with primary EHNL (HL, Lymphocyte rich type lymphoma, stage IE) in Waldeyer's ring, received chemoradiotherapy and disease free more than 2 years. Axial contast-enhanced CT images (a and b) show well-defined, regular shaped, mildly homogeneous enhanced mass affected bilateral tonsils, nasopharynx and base of tongue.

Table 1: Patients' Demographics and Clinical Findings

Total number of patients, n (%)	69
Age, years, mean ± SD, (range)	59.3 ± 17 (18-87)
Gender, n (%)	
Female	30 (43.5)
Male	39 (56.5)
Lymphoma type/subtype, n (%)	
Hodgkin's lymphoma (HL)	2 (2.9)
Non-Hodgkin's lymphoma (NHL)	67 (97.1)
Diffuse large B-cell	33 (47.8)
Marginal zone	12 (17.4)
Follicular	10 (14.5)
Small lymphocytic	5 (7.2)
Mantle cell	3 (4.3)
Natural killer/T-cell	2 (2.9)
Undetermined	2 (2.9)
Presenting symptoms, n (%)	
Mass swelling	45 (65.2)
Dyspnea	21 (30.4)
Pain	11 (15.9)
Dysphagia	13 (18.8)
B symptoms	9 (13)
Mass location-related symptoms	
Exophthalmia	5 (7.2)
Odynophagia	3 (4.3)
Trismus	2 (2.9)
Diplopia	1 (1.4)
Nasal obstruction	1 (1.4)
Serum lactate dehydrogenase (LDH) level, IU/L, mean, (range)	389 (149-2540)
Beta 2 microglobulin, µg/mL median (range)	3 (2-7)
Treatment type, n (%)	
Chemotherapy	51 (73.9)
Chemotherapy +radiotherapy	8 (11.6)
Undetermined	10 (14.5)
Prognosis, n (%)	
Lost to follow-up	4 (5.8)
Exitus	13 (18.8)
Still alive	52 (75.4)
Alive and disease free more than 2 years	50 (72.5)
Exitus or relapse within 2 years	15 (21.7)
Imaging techniques, n (%)	
CT	61 (88.4)
MRI	3 (4.3)
CT and MRI	5 (7.2)

CT: computed tomography; MRI: magnetic resonance imaging

μg/mL), respectively, which were above the normal limits. A combination chemoradiotherapy was performed in 8 cases, and chemotherapy alone was performed in 51 patients. Of the 69 patients, 61 underwent CT scan, 3 underwent MRI scan, and 5 underwent both CT and MRI scans. During the follow-up period, 13 (18.8%) patients died, 4 were lost to follow-up, and 52 were alive. The patients' demographics and clinical findings are presented in Table 1.

Tumor Characteristics and Imaging Features

The primary manifestation was observed in 14 patients (20.3%), and secondary extranodal involvement was observed in 55 patients (79.7%). At the time of presentation, most of the tumors were classified as stage II disease (42%) by using the Ann Arbor system. EHNLs predominantly observed in the Waldeyer's ring (60.9%) comprised the involvement of the tonsil (43.5%), nasopharynx (34.8%), and base of the tongue (11.6%). Sinonasal EHNL (13%) was observed as diffusely infiltrating lesions mostly originating from the nasal cavity, extending along the walls of the paranasal sinuses (Figure 3). Orbital EHNL (8.7%) originated mostly from the extraconal space (Figure 4). The parotid gland was detected as the most commonly affected salivary gland (Figure 5). Unusual involvement of organs, including the submandibular gland, larynx, thyroid, and premaxillary subcutaneous tissue, was also observed (Figure 6). Although extremely rare, muscle and plexus involvements were noted (Figure 7). There were 111 tumors with a mean diameter of 3.8 ± 1.7 cm. Solitary lesions were identified in 40 (58%) patients (Table 2).

Univariate analysis revealed that the radiological characteristics of tumor, including size greater than 5 cm (P = 047), ill-defined margin (P = .045), irregular shape (P = .046), presence of local invasion (P = .018), presence of necrosis (P = .047), and heterogeneous irregular contrast enhancement (P = .014), were significantly more frequent in patients with a poor prognosis (Table 3). Among the significant factors identified in univariate analysis, none were found to be significantly different between the groups in multivariate analysis (Table 4).

Table 2. Staging and Involvement Sites of Extranodal Lymphoma

Lymphoma type, n (%)	
Primary	14 (20.3)
Systemic	55 (79.7)
Ann Arbor stage, n (%)	
IE	14 (20.3)
IIE	29 (42)
IIIE	8 (11.6)
IIISE	1 (1.4)
IV	17 (24.6)
Tumor location, n (%)	
Waldeyer's ring	42 (60.9)
Tonsil	30 (43.5)
Nasopharynx	24 (34.8)
Base of tongue	8 (11.6)
Sinonasal cavity	9 (13)
Nasal cavity	8 (11.6)
Sinus cavities	6 (8.7)
Maxillary sinus	4 (5.8)
Sphenoethmoidal sinus	2 (2.9)
Orbit	6 (8.7)
Extraconal space	5 (7.2)
Lacrimal gland	1 (1.4)
Rectus lateralis muscle	1 (1.4)
Salivary glands	6 (8.7)
Parotid gland	5 (7.2)
Submandibular gland	1 (1.4)
Masticator space	3 (4.3)
Larynx	2 (2.9)
Thyroid	1 (1.4)
Brachial plexus	1 (1.4)
Premaxillary subcutaneous space	1 (1.4)
Pterygoid muscle	1 (1.4)
Masseter muscle	1 (1.4)
Extranodal multiplicity, n (%)	
Solitary	40 (58)
Multiple	29 (42)
Total number of tumors	111
Tumor size (mean ± SD)	3.8 ± 1.7cm

Table 3. Univariate Analyses of Radiological Features

	Patients at follow-up n=65 n (%)	Good clinical outcome n=50	Poor clinical outcome n=25	*P**
Tumor size				
<5 cm	45 (69.2)	29	16	**.047**
≥5 cm	20 (30.8)	11	9	
Tumor margin				
Well-defined	48 (73.8)	33	15	**.045**
Ill-defined	17 (26.2)	7	10	
Tumor shape				
Regular	41 (63.1)	29	12	**.046**
Irregular	24 (36.9)	11	13	
Local tumor invasiveness	6 (9.2)	1	5	**.018**
Presence of necrosis	5 (7.7)	1	4	**.047**
Regional lymph node involvement	54 (81.3)	31	23	**.129**
Enhancement degree				
Mild (+)	19 (29.2)	13	6	**.576**
Moderate (++)	39 (60)	22	17	
Marked (+++)	7 (10.8)	5	2	
Enhancement pattern				
Homogeneous nodular	43 (66.2)	31	12	**.014**
Heterogeneous irregular	22 (33.8)	9	13	

* P < .05

Discussion

The incidence of extranodal lymphomas has increased dramatically during the past 20 years compared with that of the nodal disease.[2] The head and neck region is the second most frequently involved site of extranodal lymphomas after the gastrointestinal tract. EHNL is generally diagnosed during the fifth to sixth decades of life and is more common in men.[2,4] Extranodal involvement accounted for 23% of NHL and 4% of HL of the head and neck.[4] The extranodal involvement of Hodgkin's disease has been reported to be extremely rare, with the most frequent subtypes, i.e., lymphocyte-rich and nodular sclerosis, found in 2 patients in this study.[6,8] Several studies have reported that the frequency of histological subtypes may vary depending on the tumor site. The Waldeyer's ring and paranasal sinuses are most commonly affected by *diffuse* large B-cell *lymphoma*, which is also common in oral cavity. Previous studies have reported that the marginal zone and follicular lymphomas are more frequently in the orbit and salivary glands, that was similar with our findings.[8-10]

When lymphoma is predominantly confined to an extranodal organ, with or without the involvement of adjacent lymph nodes, it is defined as primary extranodal lymphoma, whereas hematogenous dissemination of a systemic disease to an extranodal tissue is defined as secondary extranodal lymphoma. It is important to determine whether extranodal involvement represents a primary manifestation or secondary involvement, which has a poorer prognosis.[7,11]

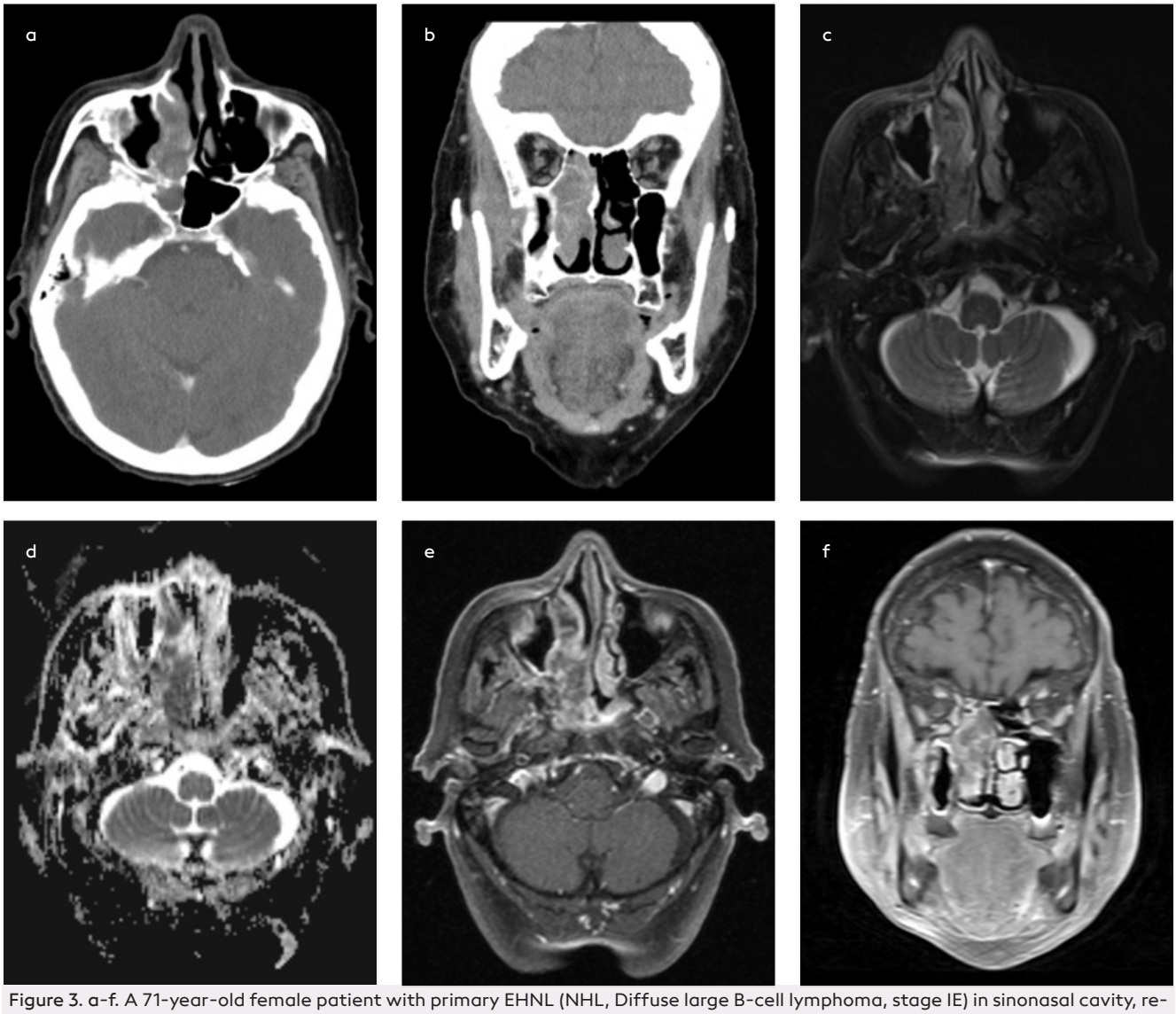

Figure 3. a-f. A 71-year-old female patient with primary EHNL (NHL, Diffuse large B-cell lymphoma, stage IE) in sinonasal cavity, received chemoradiotherapy and relapsed 15 months. Contrast-enhanced axial (a) and coronal (b) CT images show a well-defined, irregular shaped soft tissue mass involving the right side nasal cavity, posterior ethmoid cells and sphenoid sinus. The mass lesion shows hyperintense on axial fat-suppressed T2WI (c), restricted diffusion on DWI (d) and markedly heterogenous enhancement on axial and coronal contrast-enhanced T1WI (e, f).

Depending on the size of tumor and organ involvement, the symptoms of EHNL, which include swelling mass, dyspnea, dysphagia, and pain, vary significantly and may result from focal mass effect. B symptoms have been reported less frequently for EHNL than for the nodal disease.[8,9,12] Many studies in the literature have reported that EHNLs mostly originate from the Waldeyer's ring, followed by the sinonasal cavity, salivary glands, orbital cavity, thyroid, and other nonlymphoid tissues. Owing to the presence of submucosal lymphatic tissues surrounding the Waldeyer's ring, multiple sites including the tonsils, nasopharynx, and base of the tongue are usually affected.[13-16] Sinonasal involvement presents with a large infiltrating mass and most commonly arises from the nasal cavity and lateral sinus wall. Natural killer (NK)/T cell lymphoma, though rare but observed in one patient in this study, is typically seen as a mass lesion spreading and contrasting along the walls at an early stage. However, it has a more aggressive and destructive behavior in advanced stage.[16,17] In addition, the parotid gland is the most commonly affected salivary gland by lymphoma, and solitary, multifocal, or diffuse involvement may be observed.[14,18] Moreover, orbital involvement is most commonly seen as a soft tissue mass in the superolateral section of the extraconal area, and it is frequently accompanied by lacrimal gland involvement.[15,16,19] In this study, similar epidemiological and clinical features to those reported in the literature were observed.

Rare involvement of organs in the head and neck region such as the submandibular gland, larynx, and thyroid was also reported in this study. It has been reported that primary thyroid lymphomas and rare thyroid neoplasms have a strong relationship with autoimmune thyroiditis.[14,16,20] In our study, primary thyroid lymphoma was found in an elderly female patient with autoimmune thyroiditis, and the clinical and histological findings were in accordance with those of previous studies.

EHNL can originate or infiltrate any anatomical space including the muscles, bones, or nerve fibers. Musculoskeletal lymphomas are rare entities, representing 1.5%-5% of extranodal lymphoma cases, and to date, only a few cases have been reported in literature. Owing to contiguous spread from adjacent tissues, most

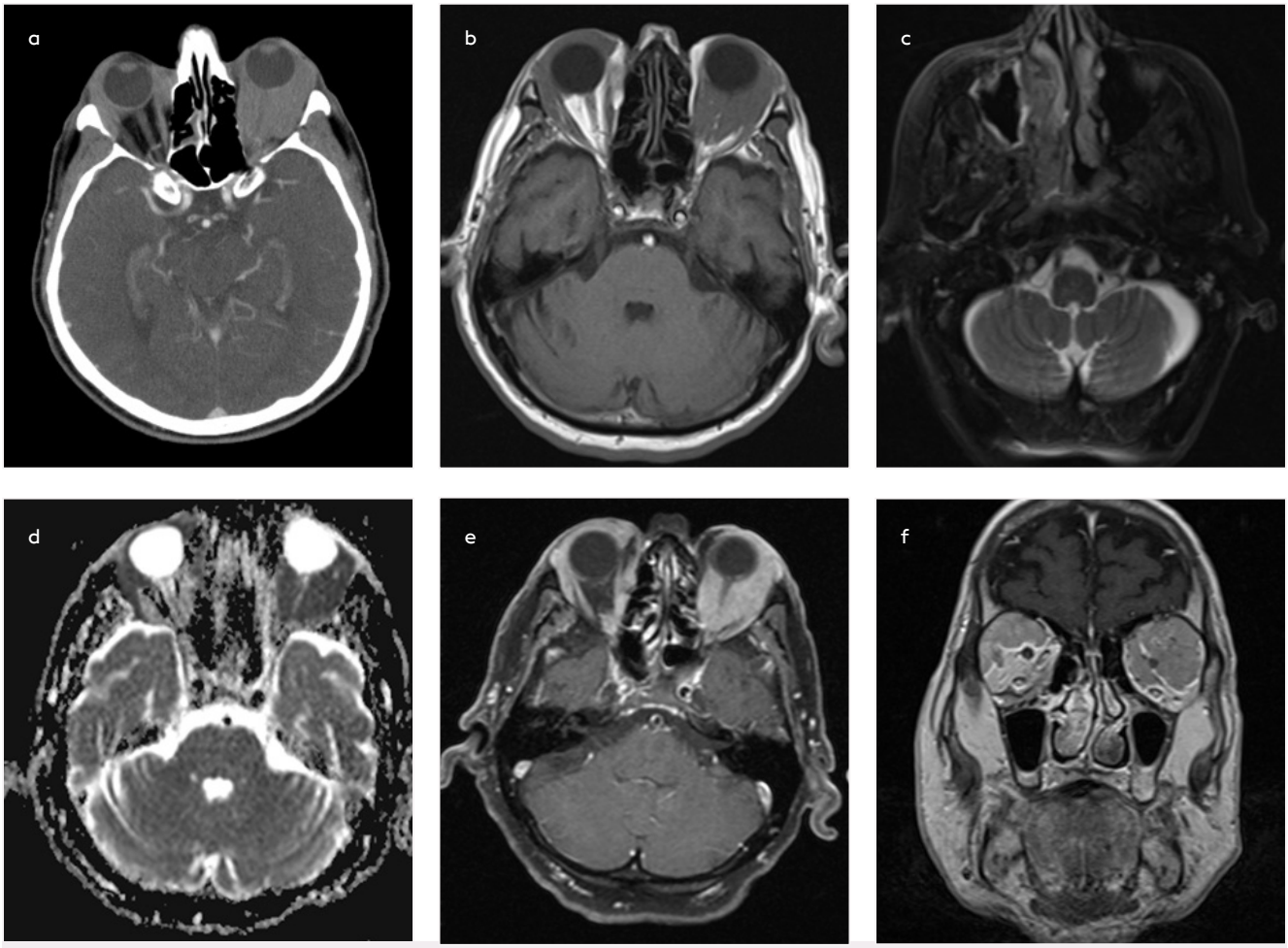

Figure 4. a-f. A 79-year-old male patient with primary EHNL (NHL, Marginal zone lymphoma, stage IE) in bilateral orbital space, received chemotherapy and disease free more than 2 years. Contrast-enhanced axial (a) CT image shows a well-defined, regular shaped soft tissue masses involving the bilateral orbital extraconal area. The mass lesions show hypointense on axial T1WI (b), isointense on axial fat-suppressed T2WI (c), restricted diffusion on DWI (d) and markedly homogeneous enhancement on axial (e) and coronal (f) contrast-enhanced T1WI.

musculoskeletal lymphomas are not the primary tumor.[16,21] Neurolymphomatosis is an extremely rare uncommon neurological manifestation characterized by the infiltration of the peripheral nervous system by lymphoma that may affect the plexus, nerve roots, and peripheral or cranial nerves. The diagnosis of neurolymphomatosis is based on the presenting symptoms, nerve enlargement and enhancement on imaging studies, and lymphoma cells in the cerebrospinal fluid or extraneural sites.[22,23]

Recent advances in imaging techniques have greatly facilitated our ability to define the cause and extent of tumor. While CT is the principal modality for imaging a primary lesion, MRI plays an important role in assessing tumor components and extension. Extranodal lymphomas manifest as submucosal, often bulky, lobulated masses covered by intact mucosa that rarely ulcerate. The presence of infiltration or lytic bone destruction is more common in aggressive lymphomas. Unlike carcinomas, ulceration, calcification, hemorrhage, or significant necrosis or cystic changes are not frequently encountered. Contrast enhancement is usually slight, but less commonly, moderate-to-marked in degree depending on the presence of increased vascularity.[14-16] In accordance with previous study findings, the results of the present study have demonstrated that imaging features favoring EHNLs include extranodal tissue involvement with intact mucosa; absence of hemorrhage, necrosis, or destruction; and presence of infiltration and mild-to-moderate contrast enhancement.

To date, a few studies have investigated the influence of radiological features on the prognosis of extranodal head and neck involvements. Chi et al.[12] reported that cervical lymphadenopathy may have poor influence on prognosis. Kim et al.[24] found that local tumor invasiveness is an important prognostic factor

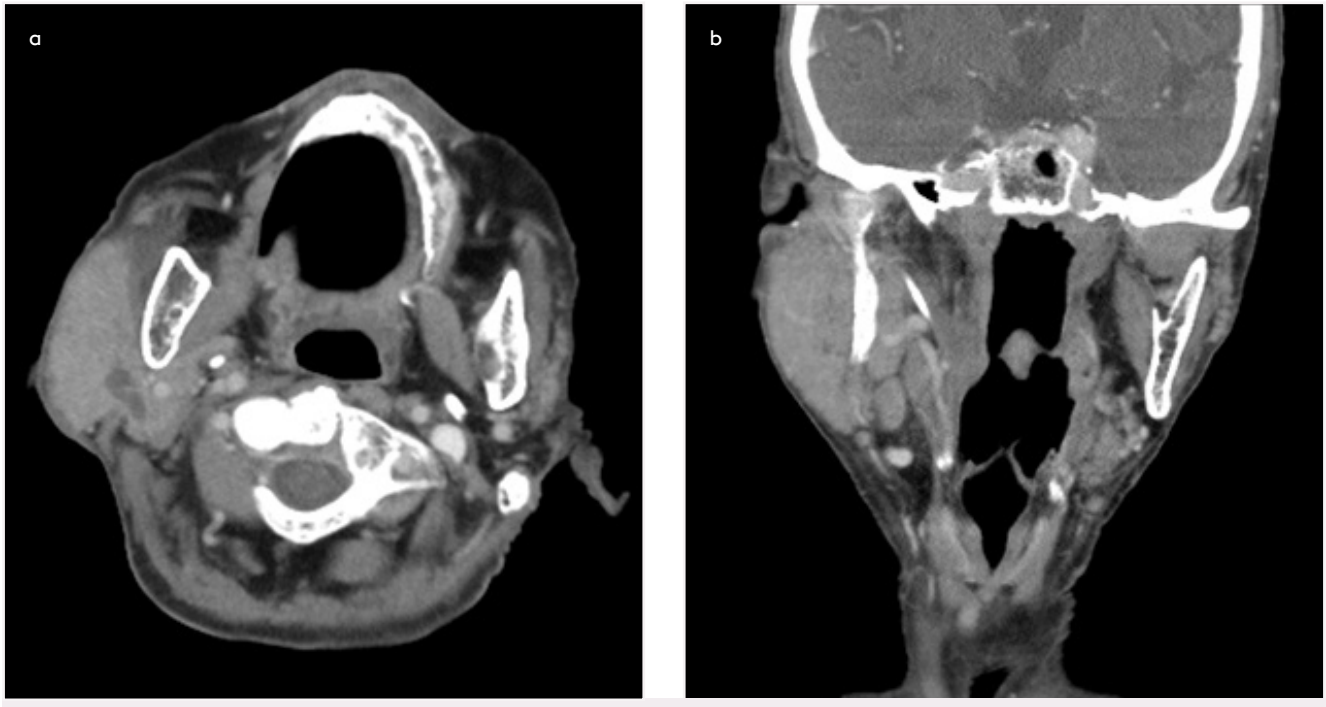

Figure 5. a, b. A 81-year-old female patient with primary EHNL (NHL, Marginal zone lymphoma, stage IE) in right side parotid gland, received chemoradiotherapy and disease free more than 2 years. Contrast-enhanced axial (a) and coronal (b) CT images show a well-defined, regular shaped, moderately homogeneous enhanced soft tissue mass involving the right side parotid gland.

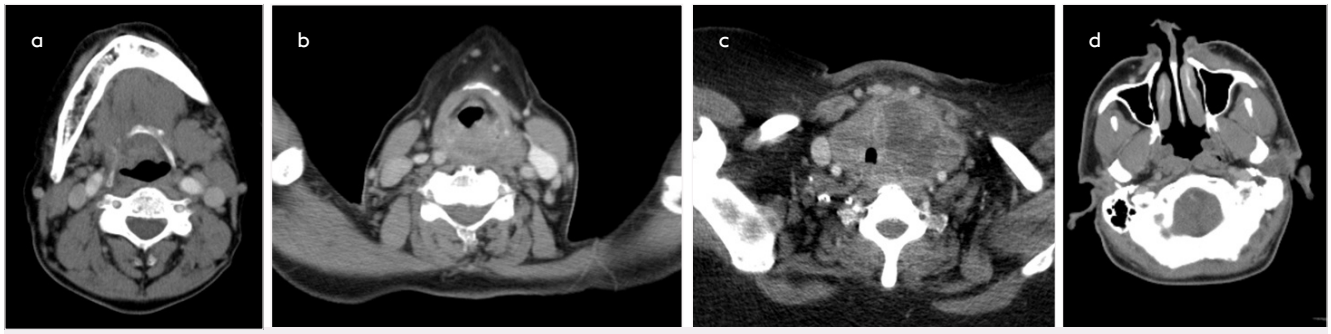

Figure 6. a-d. Unusual organ involvements by Non-Hodgkin lymphomas Axial contrast-enhanced CT images show secondary involvement of left side submandibular gland (a), secondary involvement of larynx (b), primary involvement of thyroid (c), primary involvement of premaxillary subcutaneous tissue (d).

for patients with stage IE/IIE extranodal NK/T-cell lymphoma, nasal type. A recently published study by Zhou et al.[25] revealed that CT and MRI features in patients with untreated EHNL, including tumor size, margin, shape, and local tumor invasiveness, were associated with poor clinical outcomes in univariate analysis, and only the lesion margin was found to be an independent risk factor for clinical outcome in multivariate logistic regression analysis. In the present study, univariate analysis revealed that radiological features including size (greater than 5 cm), margin (ill-defined), shape (irregular), presence of local invasion, presence of necrosis, and contrast enhancement (heterogeneous irregular) were significantly more frequent in patients with a poor prognosis. However, when these significant factors were evaluated using multivariate analysis, none of them were found to be significantly different between the groups. This may be because of the variability of disease stage and tumor histopathology in all patients.

Our study has several limitations, the first of which is its retrospective nature. Second, only a relatively small number of patients with heterogeneous clinical and tumor characteristics were enrolled. Third, different imaging techniques were used. Only 5 patients underwent both CT and MRI examinations, whereas others underwent either CT or MRI. Fourth, different histological lymphoma subtypes were involved, which may have different clinical manifestations and treatment plans. Fifth is the lack of a control group or other head and neck tumors in differential diagnosis.

In conclusion, EHNL still represents a diagnostic and management challenge due to its nonspecific clinical features and lack of pathognomonic imaging findings. Imaging techniques play a crucial role in differential diagnosis and accurate management. EHNL presents with various clinical manifestations depending on size and location. The imaging features of EHNL including tumor size, ill-defined margin, irregular

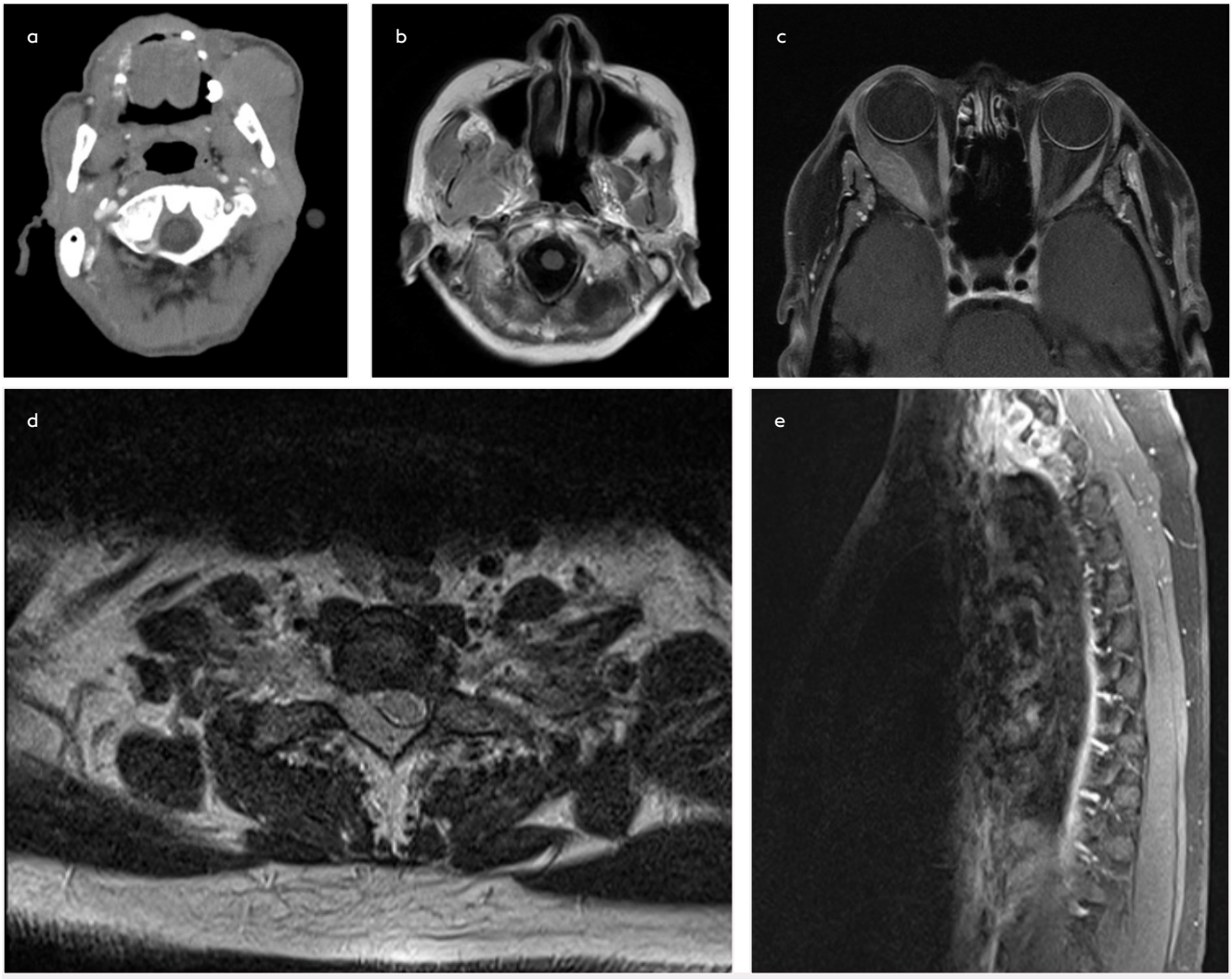

Figure 7. a-e. Muscles and plexus involvements by Non-Hodgkin lymphomas Axial contrast-enhanced CT image demonstrate secondary involvement of left side masseter musle (a). Secondary involvement of the right side masticator space with pterygoideus muscles (b) and secondary involvement of right side lateral rectus muscle (c) are shown on axial contrast-enhanced T1WIs. Axial (d) and sagittal (e) contrast-enhanced T1 weighted images show secondary involvement of right brachial plexus.

shape, presence of local invasion, presence of necrosis, and heterogeneous irregular enhancement are associated with poor outcomes. The knowledge of the most common clinical and imaging findings of EHNL will persuade clinicians and radiologists to place lymphoma at or near the top of differential diagnosis, leading to more accurate and timely diagnosis, appropriate treatment, proper disease management, and prevention of unnecessary surgery.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of the Eskisehir Osmangazi University (November 27, 2018, IRB number: 25403353-050).

Informed Consent: Written *informed consent was obtained from all patients who participated in this study.*

Peer-review: Externally peer-reviewed.

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