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# Lung hilar Ga-67 uptake in patients with lymphoma following chemotherapy

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Scintigraphic characteristics of lung hilar Ga-67 uptake (HU) and their relationship with the etiology (benign vs. malignant) of the hilar lesions in lymphoma patients following chemotherapy were retrospectively investigated. A total of 161 lymphoma patients were included in the study. The presence/absence of HU and if present, symmetry/asymmetry and intensity of HU (on the basis of a 3 scale grading system) were visually and semiquantitatively assessed on transaxial sections of thorax Ga-67 SPECT. By drawing ROIs over right and left hilum, asymmetry index (AI%) was also calculated. HU was categorized as benign or malignant depending on the radiological correlation and clinical follow-up. In the malignant group, the majority of patients (85.7%) had grade 2 or grade 3 uptake and all had asymmetric pattern. However, in the benign group, grade 1 uptake was more common (66%) and was mainly symmetric (94.6%) in appearance. AI% in the malignant group (73.7 ± 36.6) was significantly higher than in the benign group (5.7 ± 4.9) confirming the marked asymmetry in malignant patients.

**Key words:** Ga-67 scan, hilar uptake, lymphoma, scintigraphy, asymmetry index

## INTRODUCTION

GALLIUM SCANNING has an important role in the evaluation of lymphoma patients following chemotherapy or radiotherapy since other radiographic modalities such as computerized tomography (CT) have limitations in differentiating fibrosis and active residual disease after treatment. On the other hand, there are some points to be carefully evaluated when interpreting Ga-67 images following therapy. One of these is positive lung hilar Ga-67 uptake which might be either due to residual/recurrent active disease or because of a benign inflammatory response in the hilum which might be attributed to a treatment effect. Differentiating the etiology of hilar Ga-67 uptake (whether it is benign or malignant) would result in a change in the clinical management of the patients.

The purpose of this retrospective study is to evaluate the scintigraphic patterns including symmetry/asymmetry and the intensity of hilar Ga-67 uptake following chemotherapy and to investigate their relationship with the etiology (benign versus malignant) of the hilar involvement.

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## MATERIALS AND METHODS

*Patients*

We retrospectively reviewed Ga-67 studies of patients with pathologically confirmed diagnosis of Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL) treated between June 1996 and December 2002 in our institution. One hundred sixty-one patients who had Ga-67 study after receiving at least 3 cycles of chemotherapy regimen were included in the study majority of the patients had more than one Ga-67 scan. The first Ga-67 scan following chemotherapy was the primary scintigraphy on which scintigraphic characteristics of lung hilar uptake has been investigated. There was at least a 3-week interval between the last chemotherapy administration and Ga-67 injection, except for 3 patients with 7–10 days interval. Both whole body and thorax single photon emission computed tomography (SPECT) Ga-67 images of the patients were examined. The following information on each patient was retrospectively obtained from the

**Table 1** Characteristics of patients with hilar uptake (Group A)

| Patient | Sex | Age at diagnosis | Diagnosis | Chemotherapy regimen | Total no. of chemotherapy cycles | Etiology of HU (malignant/ benign) |
|---|---|---|---|---|---|---|
| 1 | M | 47 | NHL | CHOP, Other | 14 | m |
| 2 | M | 56 | HD | ABVD | 6 | b |
| 3 | M | 44 | HD | ABVD | 3 | b |
| 4 | M | 32 | HD | ABVD | 4 | b |
| 5 | F | 39 | HD | ABVD | 3 | b |
| 6 | F | 54 | NHL | CHOP | 4 | b |
| 7 | F | 74 | NHL | CHOP | 6 | b |
| 8 | F | 62 | NHL | ABVD, Other | 5 | m |
| 9 | M | 43 | NHL | CHOP, Other | 9 | b |
| 10 | M | 53 | HD | ABVD | 6 | b |
| 11 | M | 7 | HD | COPP, ABVD | 12 | m |
| 12 | M | 33 | HD | ABVD | 6 | b |
| 13 | F | 59 | NHL | CVP | 6 | b |
| 14 | M | 55 | NHL | CHOP | 5 | b |
| 15 | F | 69 | NHL | CHOP | 6 | b |
| 16 | M | 38 | NHL | CHOP | 4 | b |
| 17 | M | 59 | HD | ABVD | 6 | b |
| 18 | F | 48 | NHL | CHOP | 8 | b |
| 19 | F | 44 | NHL | CHOP, Other | 8 | m |
| 20 | M | 19 | HD | ABVD | 6 | b |
| 21 | F | 24 | HD | ABVD | 6 | b |
| 22 | F | 44 | NHL | CHOP | 6 | b |
| 23 | M | 46 | HD | COPP | 6 | b |
| 24 | M | 40 | HD | COPP, ABVD | 14 | b |
| 25 | M | 46 | NHL | CHOP | 4 | b |
| 26 | M | 33 | NHL | CHOP | 6 | b |
| 27 | F | 49 | NHL | CHOP, Other | 8 | b |
| 28 | M | 35 | HD | ABVD | 6 | b |
| 29 | M | 67 | HD | COPP, ABVD | 12 | b |
| 30 | M | 32 | HD | ABVD | 4 | b |
| 31 | F | 17 | HD | ABVD | 3 | b |
| 32 | M | 65 | NHL | CHOP | 7 | b |
| 33 | M | 41 | HD | ABVD | 6 | b |
| 34 | M | 46 | NHL | CHOP | 6 | b |
| 35 | M | 41 | HD | COPP, ABVD | 10 | m |
| 36 | M | 60 | NHL | CHOP | 3 | b |
| 37 | M | 35 | HD | ABVD | 5 | b |
| 38 | F | 61 | NHL | CHOP | 6 | b |
| 39 | M | 32 | HD | COPP, ABVD | 12 | b |
| 40 | F | 68 | NHL | CHOP | 6 | b |
| 41 | F | 65 | HD | ABVD | 3 | m |
| 42 | F | 36 | HD | ABVD | 4 | b |
| 43 | M | 60 | NHL | CHOP | 4 | b |
| 44 | F | 61 | NHL | CHOP | 6 | b |
| 45 | F | 56 | NHL | CHOP | 6 | b |
| 46 | M | 41 | NHL | CHOP, Other | 13 | b |
| 47 | M | 20 | HD | COPP + ABVD, Other | 14 | m |
| 48 | M | 30 | NHL | CVP, Other | 12 | b |
| 49 | M | 39 | HD | ABVD | 5 | b |
| 50 | F | 42 | NHL | CHOP | 6 | b |
| 51 | M | 53 | NHL | CHOP | 5 | b |
| 52 | M | 39 | NHL | CHOP | 8 | b |
| 53 | M | 80 | NHL | CHOP | 6 | b |
| 54 | F | 56 | NHL | CHOP, Other | 7 | b |
| 55 | M | 61 | NHL | CHOP | 6 | b |
| 56 | F | 65 | NHL | CHOP | 6 | b |

| | | | | | | |
|---|---|---|---|---|---|---|
| 57 | F | 60 | NHL | CHOP, Other | 11 | b |
| 58 | M | 15 | HD | ABVD | 6 | b |
| 59 | M | 40 | HD | COPP | 6 | b |
| 60 | M | 22 | HD | MOPP + ABVD | 8 | m |
| 61 | F | 34 | NHL | CHOP | 6 | m |
| 62 | F | 62 | HD | CHOP | 3 | m |
| 63 | F | 18 | NHL | CHOP | 8 | m |
| 64 | M | 36 | HD | COPP, ABVD | 9 | m |
| 65 | F | 41 | NHL | CHOP | 6 | m |
| 66 | M | 39 | HD | ABVD | 6 | m |
| 67 | F | 35 | NHL | CHOP | 6 | b |
| 68 | M | 57 | NHL | CHOP | 4 | b |
| 69 | M | 45 | NHL | CHOP | 3 | b |
| 70 | F | 55 | NHL | CHOP | 6 | b |

NHL: Non-Hodgkin's lymphoma; HD: Hodgkin's disease; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; COPP: cyclophosphamide, vincristine, procarbazine, prednisone; CVP: cyclophosphamide, vincristine, prednisone; MOPP: mechloretamine, vincristine, procarbazine, prednisone; m: malignant; b: benign

**Table 2** Comparison of groups with (Group A) or without (Group B) hilar uptake

| | Age | Sex M/F | HD | NHL | Chemotherapy | | |
|---|---|---|---|---|---|---|---|
| | | | | | CHOP | ABVD | Others* |
| Group A (n = 70) | 45 ± 15 | 42/28 | 30 | 40 | 31 | 19 | 20 |
| Group B (n = 91) | 38 ± 16 | 56/35 | 45 | 46 | 40 | 31 | 20 |

Others: COPP, CVP, MOPP, additional chemotherapeutics to CHOP or ABVD and salvage chemotherapy regimens containing ifosfamide, idarubicin, etoposide, cisplatin, methotrexate, cytosine arabinoside

medical records: medical history, physical examination, chest radiograph, CT scan, Ga-67 scan, bone marrow examination, treatment details, and the clinical outcome.

*Staging of the lymphoma and treatment details*

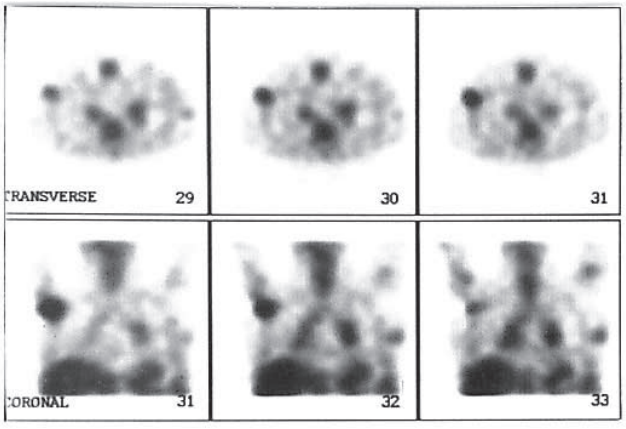
Stage of disease was determined using the Ann Arbor staging system.[1] Ann Arbor clinical Stage I or II HD patients with favorable prognostic factors received three cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by involved field radiotherapy according to a prospective trial being carried out at our institution. Patients with advanced HD received six cycles of ABVD chemotherapy. Asymptomatic patients with indolent NHLs were monitored until disease progression (watchful waiting policy) and treated subsequently after disease progression.[2] The majority of patients with aggressive NHLs were treated with standard cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy regimen.[3] The "bulky" disease sites were irradiated in addition to chemotherapy both in patients with HD and NHL. Relapsing HD and NHL patients were treated with salvage chemotherapy regimens containing ifosfamide, idarubicin, etoposide, cisplatin, methotrexate, cytosine arabinoside, or corticosteroids. Some patients responsive to salvage chemotherapy regimens proceeded to high-dose chemotherapy protocols with autologous stem cell support.

Patients received at least 3, up to 14 (median: 6) cycles of chemotherapy. Responses to chemotherapy and/or radiotherapy were determined by physical examination, laboratory studies, chest radiograph, CT, and Ga-67 scans. A complete response (CR) was defined as the total regression of lymph nodes to their normal size with no clinical, radiographic or other evidence of lymphoma after therapy. A partial response (PR) was defined as at least a 50% reduction in the sum of the products of the largest perpendicular diameters of all measurable lesions and persistently abnormal gallium scan findings. Stable disease (SD) was defined as less than a PR, with no lesion enlarging by ≥25%, and no new lesions developing.

The patient characteristics are provided in Table 1.

*Ga-67 Imaging*

Routine whole body imaging and SPECT studies were performed at 48–72 hours after injection of 296–370 MBq (8–10 mCi) Ga-67. A dual head large field gamma camera, equipped with a medium energy collimator and 20% energy window centered at 93, 185, 300 keV photopeaks was used for Ga-67 imaging. In SPECT study, a total of 64 images with 64 × 64 matrix with an acquisition time of 40 seconds per view were obtained. Acquisition time for whole body imaging was approximately 18–20 minutes (8–10 cm per minute) with the patient in the supine position. Reconstruction was performed by filtered back

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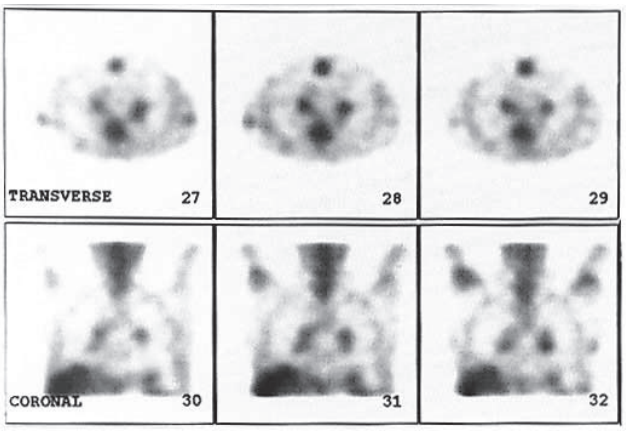


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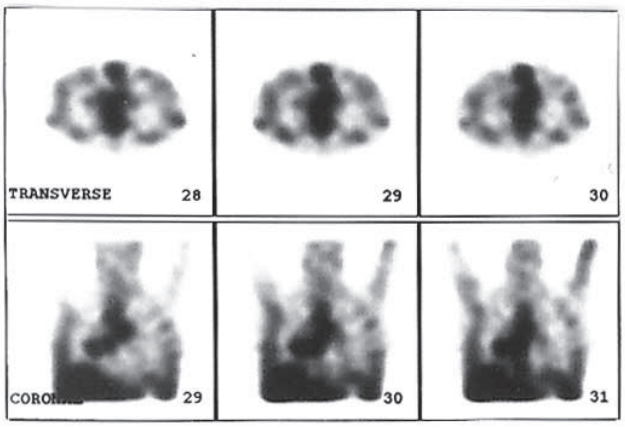
**Fig. 1** Thorax Ga-67 SPECT images of a 35-year-old male HD patient showing hilar Ga-67 uptake with benign etiology (Patient no. 37). a: In Ga-67 scan (*top row*: transverse, *lower row*: coronal views) taken after 5 cycles of ABVD chemotherapy grade 2 symmetric lung hilar uptake and increased radioactivity accumulation in the right axillar region was observed. Physical examination revealed right axillary lymph node. CT scan demonstrated enlarged lymph nodes in the right axillary region and normal findings in both hilar regions. Following Ga-67 scan the patient received salvage chemotherapy regimens and underwent autologous bone marrow transplantation. b: Ga-67 scan (*top row*: transverse, *lower row*: coronal views) taken 1 year after the initial scan, no axillary accumulation of Ga-67 was observed, but grade 2 bilateral symmetric lung hilar uptake was still present. The patient has attained a CR clinically.

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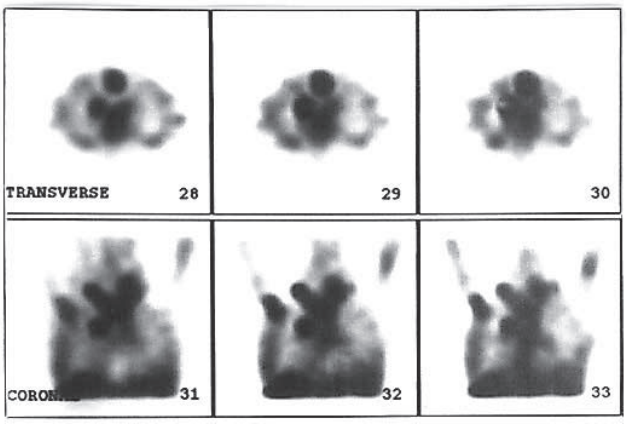


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**Fig. 2** Thorax Ga-67 SPECT images of a 34-year-old female NHL patient showing hilar Ga-67 uptake with malignant etiology (Patient no. 61). a: Ga-67 scan (*top row*: transverse, *lower row*: coronal views) taken after 6 cycles of chemotherapy and mediastinal radiotherapy revealed mediastinal and grade 2 right lung hilar uptake. b: Even after additional 2 cycles of salvage chemotherapy progression of the disease to both cervical and right axillary was observed in Ga-67 scintigraphy (*top row*: transverse, *lower row*: coronal views). The etiology of HU was categorized as malignant in this patient.

projection technique with a Butterworth filter. Attenuation correction was not used. Images in coronal, sagittal, and transaxial planes were obtained.

*Ga-67 Image Analysis*

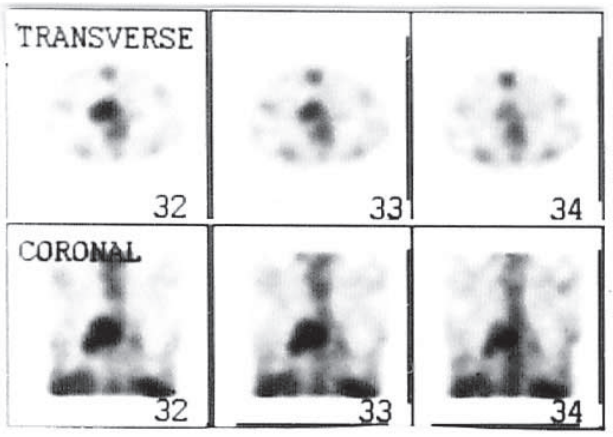
Ga-67 images were reviewed by 2 nuclear medicine physicians, and any disagreements resolved by discussion until a consensus was reached.

*a) Visual analysis*

The presence/absence of Ga-67 hilar uptake and if present, symmetry or asymmetry of uptake was decided on both whole body and thorax SPECT images. The patients were categorized into two groups based on the presence (Group A) and absence (Group B) of hilar uptake.

The degree of uptake intensity on whole body and transaxial slices of thorax SPECT images in Group A was also visually rated taking sternum as a reference area based on a 3 scale grading system.

- Grade 1: intensity lower than the sternum
- Grade 2: intensity equal to the sternum
- Grade 3: intensity higher than that of sternum

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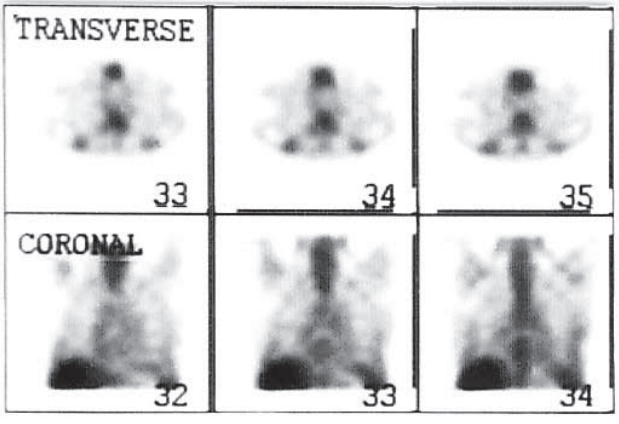


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**Fig. 3** Thorax Ga-67 SPECT images of a 41-year-old male with the diagnosis of relapsed HD (Patient no. 35). a: Ga-67 scan (*top row*: transverse, *lower row*: coronal views) taken after 6 cycles of COPP, and 4 cycles of ABVD chemotherapy revealed grade 2 asymmetric lung hilar uptake. b: The patient was referred for reevaluation 8 months after the completion of salvage chemotherapy. Ga-67 images revealed disappearance of abnormal accumulation detected on previous scan. CT scan was also normal.

*b) Semiquantitative evaluation*

By drawing ROIs over right and left hilum, asymmetry index (AI) was calculated according to the following formula: AI% = 100 × [$(a - b)/(a + b)$], where $(a - b)$ = difference between mean counts of left and right hilum, $(a + b)$ = sum of the mean counts of left and right hilum. AI% was calculated in 56 patients.

As mentioned in the literature the criteria for diagnosis of benign and malignant hilar uptake were as follows[4,5];

*For benign lesions:*

1) Ga-67 uptake in hilar region with no evidence of lymphadenopathy on CT scan,

2) Persisting Ga-67 uptake on scintigraphic follow-up, despite disappearance of all other disease sites and/or the patient has attained a CR.

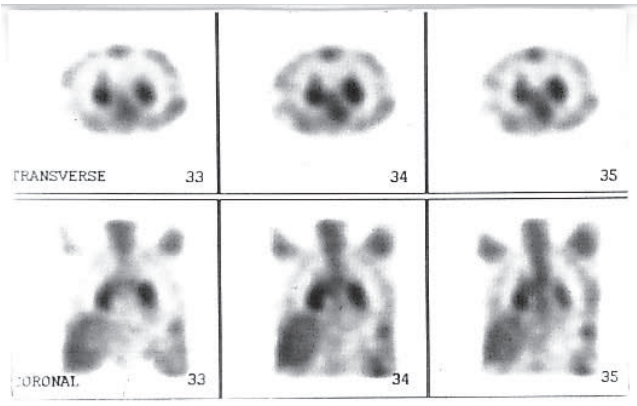


**Fig. 4** Thorax Ga-67 SPECT images (*top row*: transverse, *lower row*: coronal views) of a 67-year-old male with the diagnosis of HD (Patient no. 29). Ga-67 scan taken after the completion of total 12 cycles of chemotherapy (COPP, ABVD) revealed grade 3 symmetric lung hilar uptake although CT scan was normal, and the etiology of HU was considered as benign.

*For malignant lesions:*

1) Progressive hilar adenopathy unresponsive to therapy,

2) A Ga-67 uptake in the hilar region that disappeared when a CR was achieved,

3) A new hilar lesion with positive CT finding after a period of remission.

Patients who satisfied at least one of the above mentioned criteria were categorized in the benign or malignant group.

Patients whose data were inconclusive for deciding whether the lesion in hilus was benign or malignant were excluded from the study.

## RESULTS

*Patients*

A total of 86 NHL, 75 HD were studied. The mean age at time of diagnosis was 45 years, ranging from 7 to 80 years. Ninety-eight patients were male (60.9%), and 63 were female (39.1%).

Mediastinal radiotherapy was employed in 3 of 70 (4.3%) patients in Group A. The distribution of lymphoma stage in Group A was as follows: stage-I; 3 (4.3%), stage-II; 27 (38.6%), stage-III; 14 (20%), and stage-IV; 11 (15.7%). In 15 (21.4%) patients the stage of the disease remained undetermined.

*Scintigraphic patterns of Ga-67 study*

Lung hilar uptake was positive in 70 of 161 (43.5%: Group A) patients, however no gallium accumulation on the hilar regions detected in the remaining 91 (56.5%: Group B) cases.

No statistical differences in terms of age, sex, type of lymphoma, or chemotherapy regimens were found

**Table 3** Scintigraphic appearances of hilar uptake in Group A

| | Grade of HU | | | S | A | AI% (Mean ± SD)* |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | | | |
| Benign (n = 56) | 37 | 11 | 8 | 53 | 3 | 5.7 ± 4.9 |
| Malignant (n = 14) | 2 | 6 | 6 | 0 | 14 | 73.7 ± 36.6 |

S: Symmetric hilar uptake, A: Asymmetric hilar uptake by visual analysis, AI: Asymmetry index
*$p < 0.05$ (benign vs. malignant)

between Group A and Group B ($p > 0.05$, Table 2).

In 32 (45.7%) patients in Group A, hilar uptake was present only on thorax SPECT images.

Increased gallium uptake in bony structures which might be attributed to the chemotherapy effect was evident in 7 (markedly in 5) cases of Group A.

In Group A, the timing for Ga-67 scan following chemotherapy was as follows: at the end of 3 cycles: 21 patients, at the end of 4–6 cycles: 30 patients, at follow-up: 19 patients. The etiology of hilar uptake was benign in 56 of 70 (80%) and malignant in the remaining 14 (20%) cases in Group A (Figs. 1–3). Mediastinal extention from hilar region was observed in 4 (28.6%) of the patients in the malignant group. In the malignant group, the majority of patients had either grade 2 or grade 3 uptake (12 of 14: 85.7%) which showed asymmetric pattern in all. However, in the benign group, grade 1 uptake was more common (37 of 56: 66%) and mainly symmetric (53 of 56: 94%) in appearance. The mean of AI% in the malignant group was significantly higher than of the benign group confirming the marked asymmetry in malignant patients (73.7 ± 36.6% vs. 5.7 ± 4.9%, $p < 0.05$, Table 3).

## DISCUSSION

Although FDG-PET has gained wide acceptance for evaluation of patients with lymphoma, Ga-67 imaging still remains the preferred imaging study in many nuclear medicine departments due to its lower cost and being technically less complex than FDG-PET.[6,7] On the other hand, false positive gallium uptake in pulmonary hila without corresponding clinical and/or CT evidence of hilar lymphoma in treated patients has been frequently reported.[4,8–11] This problem seems to be increasing since the doses of gallium injected (111 vs. 370 MBq: 3 vs. 10 mCi) and the use of thoracic gallium SPECT examination have recently increased compared to previous studies. The most important issue with hilar gallium uptake in treated lymphoma patients is the differentiation of benign post-therapeutic changes from residual or recurrent active disease. Therefore, it is important to know the scintigraphic patterns of hilar uptake which might be helpful for such differentiation. In this regard, we investigated the prevalence and scintigraphic patterns of hilar gallium uptake in 161 treated lymphoma patients.

In this study, we observed HU in 70 of 161 (43.5%) treated lymphoma patients with 32 of 70 (45.7%) present on SPECT only. Due to the better imaging characteristics, it is an expected finding to find a higher frequency with SPECT compared to planar studies. The prevalence of HU in lymphoma patients in the literature showed great variation ranging from 47–85%.[4,5,10–12] The wide variation between these numbers in the literature may be due to several reasons including the different techniques and gallium doses used (planar vs. SPECT, and 3 vs. 10 mCi), the inhomogenities of the time interval following therapy and gallium study, and differences in the patient population studied.

In the present study, the etiology of hilar uptake was benign in most of the cases (56 of 70: 80%) and malignant in the remaining patients (14 of 70: 20%). Our results are in concordance with previous investigators.[4,5,11,12] The most important characteristics of benign HU were being generally symmetric (53 of 56: 94.6%) and lower intensity than that of sternum (grade 1 uptake, 37 of 56: 66%). On the other hand, the characteristics of malignant group were quite different since the majority of patients with malignant HU had grade 2 or grade 3 uptake (12 of 14: 85.7%) and all had asymmetric appearance.

To compare the uptake intensity of HU, sternum was chosen as a reference anatomic region as indicated in the literature.[12] Since sternum and pulmonary hilar regions are always included in the same or adjacent planes on thoracic SPECT slices, selection of the sternum provided a practical reference for comparison. We are aware of the fact that, radiogallium accumulation may increase in bony structures following chemotherapy resulting in difficulty in proper comparison. On the other hand, there was only 5 patients in Group A with marked bony gallium uptake. Concentration of gallium uptake in mediastinal and hilar regions has been quantified by Evan-Sapir et al. to determine a threshold value reliably distinguishing lymphoma from benign uptake.[5] These authors concluded that in patients with active lymphoma, the gallium concentration was significantly greater than that in benign hilar uptake ($13.2\% + 5.4\% \times 10^{-3}$ injected dose/m*l* vs. $5.6\% + 1.5\% \times 10^{-3}$). Although, quantitative measurement is considered to be very sensitive for differentiation between benign vs. malignant hilar uptake, it is not practical for most nuclear medicine departments with hectic schedule and limited facilities. On the other hand, simple visual assessment or semiquantitative assessment

like ours can be used instead.

To evaluate symmetry of HU in a semiquantitative manner, AI% (asymmetry index) of HU was also calculated in the present study which, to our knowledge, has not been reported before. Higher values of AI% confirming the marked asymmetry in the malignant group compared to benign HU were found in our study (73.7 ± 36.6% vs. 5.7 ± 4.9%, $p < 0.05$). In some cases, it might be difficult to decide visually upon symmetry/asymmetry of HU particularly for inexperienced readers. Regarding this, AI% is an objective and easily calculated index which might be helpful to differentiate benign from malignant etiology.

All HU seen in 70 of our patients can not be attributed to treatment effect, as in the literature it has been shown that HU is a common finding even prior to chemotherapy.[4,11,13] Since not all of the patients with HU in our study underwent basal scintigraphy, the real contribution of treatment to the prevalence of HU detected after therapy can not be elucidated. Frohlich et al. reported that HU might be seen as early as after the first cycle of CHOP and persisted a median of 27 months from onset. The same authors also concluded that HU is independent of CHOP dosage.[4] We could not investigate the length of time that HU persisted after chemotherapy since the timing of the follow-up gallium study showed great variation.

In conclusion, lung HU is a common finding in patients with lymphoma following chemotherapy and frequently benign in origin, particularly if HU is symmetric and its intensity is less than that of sternum. Asymmetry index (AI%) as proposed in the present study can be used when visual assessment for the symmetry of HU is inconclusive.

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