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Usefulness of ^{67}Ga scintigraphy in extranodal malignant lymphoma patients

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Objective: ^{67}Ga scintigraphy has a well-documented role in nodal lymphoma for both disease staging and assessment of treatment response. The objective of the present study was to examine the role of ^{67}Ga scintigraphy in diagnosis and assessment of treatment response, in patients with extranodal malignant lymphoma. ***Methods:*** Seventy-one patients with extranodal malignant lymphoma were studied. Whole body scans in all and SPECT scans in some selected patients were performed 72 hours after injection of ^{67}Ga-citrate. The influence of tumor site, histological classification and tumor size on ^{67}Ga scintigraphy sensitivity was analyzed. Twenty-one of the seventy-one patients also had a second ^{67}Ga scintigraphy to assess response to treatment. ***Results:*** The overall ^{67}Ga scintigraphy sensitivity was 83.1% (59/71). The sensitivity was low in patients whose extranodal lymphoma occurred in skin (0/3) and urinary bladder (0/1), as compared to other tumor sites. According to the histological classification of the lesion, the sensitivity was lower in low-grade than in intermediate and high-grade lymphoma. According to the tumor size, the sensitivity was low in lesions less than 2 cm in diameter than those more than 2 cm in diameter. The results changed from positive to negative accumulation in 20 (95.2%) of the 21 patients who had ^{67}Ga scintigraphy to assess the response to treatment. These 20 patients showed a good clinical course. ***Conclusions:*** Although ^{67}Ga scintigraphy did not show positive accumulation in patients with skin and urinary bladder lymphoma, it was helpful to confirm the diagnosis and to evaluate the therapeutic effect in most patients with extranodal malignant lymphoma.

Key words: extranodal malignant lymphoma, ^{67}Ga scintigraphy, therapeutic effect

INTRODUCTION

ALTHOUGH LYMPHOMAS are usually considered to be tumors of lymph nodes, their extranodal manifestations are well recognized and occur in 20% to 30% of lymphoma patients.[1] Many studies have shown the clinical relevance of gallium-67 (^{67}Ga) scintigraphy in patients with Hodgkin's disease or non-Hodgkin's lymphoma.[2–6] There are sporadic case reports that ^{67}Ga accumulates in extranodal lymphoma.[7–9] However, whether or not ^{67}Ga scan is a reliable method for the diagnosis of extranodal lymphoma is not established. Furthermore, the role of ^{67}Ga scintigraphy in assessing the treatment response has not been clarified in extranodal lymphoma.

With the increasing availability of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), many practitioners are turning from ^{67}Ga to ^{18}F-FDG PET for evaluating lymphoma, with the opinions that interpretation of ^{18}F-FDG PET is more rapid and timely (1 day as opposed to 3–7 days) and that ^{18}F-FDG PET scans are easier to read than ^{67}Ga scans.[10–12] Although ^{67}Ga certainly has limitations in evaluating lymphoma, good, reproducible research has been done for years since Edwards and Hayes[2] first described the accumulation of ^{67}Ga in the lymph nodes of a patient with Hodgkin's disease. Until the predictive value for extranodal lymphoma is clearly established, and until ^{18}F-FDG PET is available at all centers, many practitioners will continue to rely on ^{67}Ga in evaluating extranodal lymphoma.

The objective of the present study was to examine the role of ^{67}Ga scintigraphy in diagnosis and assessment of

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treatment response, in patients with extranodal malignant lymphoma.

MATERIALS AND METHODS

Patients

Seventy-one consecutive patients (41 males, 30 females; mean age, 66 ± 19 yrs; age range, 32–85 yrs) who had primary extranodal malignant lymphoma and had undergone ^{67}Ga scintigraphy at our hospital between July 1990 and March 2002 were examined retrospectively. No patients had received any treatment or biopsy before the ^{67}Ga scintigraphy. Tumor sites for all cases are listed in Table 1. Lymphomas from all extranodal sites that normally contain no lymphoid tissue were considered. The main sites in decreasing order of frequency were thyroid, stomach, breast, bone and soft tissue, paranasal sinus and central nervous system. The histological classification of the tumor was available in 57 patients. Histological classification of lymphoma was performed according to the International Working Formation guidelines.[13] They were diagnosed as having non-Hodgkin's lymphoma including: high grade in 11, intermediate grade in 35, and low grade in 11. Of the remaining 14 patients, histological classification was not available due to histological examination having been performed at a different hospital and unavailability of the relevant data. Tumor size was obtained from CT imaging measurements. The tumor size ranged from 1.5–7.0 cm. The influence of tumor site, histological classification and tumor size on ^{67}Ga scintigraphy sensitivity was analyzed. Twenty-one patients also had a second ^{67}Ga scintigraphy to assess response to treatment 2 weeks after completion of therapy.

Informed consent was obtained from each patient at the time of scintigraphy.

^{67}Ga scintigraphy

^{67}Ga scintigraphy was performed using 111–148 MBq ^{67}Ga-citrate. Whole body and spot images were taken 72 hours after injection. Imaging was performed with a large field of view gamma camera (Prism 2000; Picker International, Cleveland, OH, GCA-90B; Toshiba, Tokyo, Japan, Ω500; Aloka, Tokyo, Japan) with medium-energy and general purpose collimator. Twenty-percent windows were placed symmetrically around each of the three main photopeaks of ^{67}Ga (93, 184 and 296 keV). Whole body imaging was performed with both anterior and posterior view images at a speed of 15 cm/min. The spot images were obtained by collecting 300–500 k counts at the preset time of 5 min. When necessary, single photon emission computed tomography (SPECT) was performed only in selected patients, mainly in cases in which it was necessary to better locate abnormalities visualized only on planar images. SPECT was performed on a 64 × 64 matrix at 120° at 30 sec each over a range of 360°. Image reconstruction was done using filtered backprojection with a Ramp filter. Transverse, coronal and sagittal sections were reconstructed. Only intense abnormal accumulation clearly separated from normal structures was considered positive. ^{67}Ga uptake only in regions of normal, physiologic activity was considered negative.

Table 1 Sensitivity on ^{67}Ga scintigraphy according to tumor site in patients with extranodal lymphoma

Tumor Site	Sensitivity*		
	Planar	SPECT	Overall
Central nervous system	100% (4/4)	100% (4/4)	100% (4/4)
Orbit	100% (2/2)	100% (2/2)	100% (2/2)
Thyroid	94.1% (16/17)	n.d.	94.1% (16/17)
Paranasal sinus	66.7% (4/6)	66.7% (4/6)	66.7% (4/6)
Salivary glands	100% (2/2)	n.d.	100% (2/2)
Pharynx	100% (1/1)	100% (1/1)	100% (1/1)
Breast	100% (7/7)	100% (5/5)	100% (7/7)
Mediastinum	100% (1/1)	100% (1/1)	100% (1/1)
Chest wall	100% (2/2)	100% (1/1)	100% (2/2)
Lung	100% (1/1)	100% (1/1)	100% (1/1)
Esophagus	100% (1/1)	100% (1/1)	100% (1/1)
Stomach	57.1% (8/14)	50% (3/6)	64.3% (9/14)
Rectum	100% (1/1)	n.d.	100% (1/1)
Pancreas	0% (0/1)	100% (1/1)	100% (1/1)
Urinary bladder	0% (0/1)	0% (0/1)	0% (0/1)
Skin	0% (0/3)	n.d.	0% (0/3)
Bone and soft tissue	100% (7/7)	100% (3/3)	100% (7/7)
Total	80.3% (57/71)	81.8% (27/33)	83.1% (59/71)

* Number in parentheses indicated number of patients.
n.d. = not done

Table 2 Sensitivity on ^{67}Ga scintigraphy according to histological classification in patients with extranodal lymphoma

Tumor Grade	Sensitivity *
Low	45.5% (5/11)
Intermediate	88.6% (31/35)
High	100% (11/11)
Unclassified	85.7% (12/14)

* Number in parentheses indicated number of patients.

Table 3 Sensitivity on ^{67}Ga scintigraphy according to tumor size in patients with extranodal lymphoma

Tumor Size	Sensitivity*
2 cm ≥	36.4% (4/11)
4 cm >	94.1% (32/34)
4 cm ≤	88.5% (23/26)

* Number in parentheses indicated number of patients.

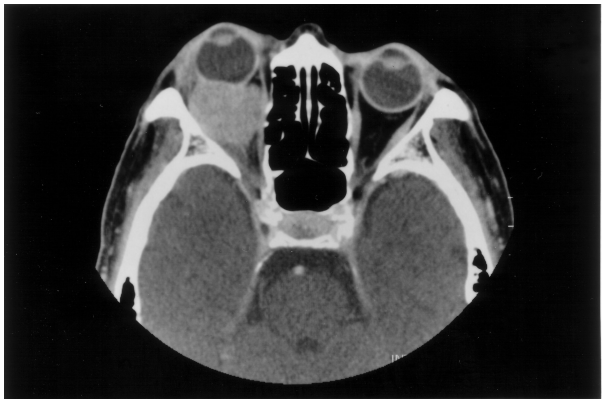
Treatment

Treatment comprised chemotherapy, radiotherapy alone, or a combination of the two. Chemotherapy consisted of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), either as one unit or in various combinations of the four drugs, for three to eight cycles. Radiation treatment was performed according to institutional guidelines with a radiotherapy dose necessary for local tumor control (e.g., 40–60 Gy) depending on tumor histology and stage. Chemotherapy may suppress uptake of ^{67}Ga by an active lymphoma for a few days after administration. ^{67}Ga was, therefore, injected 2 weeks after the end of the cycle of chemotherapy. At this time, chemotherapy does not appear to affect ^{67}Ga uptake.[14] After treatment, disappearance of abnormal accumulation was considered a negative result.

RESULTS

Table 1 presents the sensitivity on ^{67}Ga planar scintigraphy and ^{67}Ga SPECT according to the locations of primary extranodal lymphoma in all patients examined. The total overall ^{67}Ga scintigraphy sensitivity was 83.1% (59/71). The sensitivity was the lowest in patients whose extranodal lymphoma occurred in skin (0%) and urinary bladder (0%) as compared to other tumor sites. According to the histological classification of the lesion, the sensitivity was lower in low-grade than in intermediate and high-grade lymphoma (Table 2). According to the tumor size, the sensitivity was lower in lesions less than 2 cm in diameter than those more than 2 cm in diameter (Table 3).

In four patients, the ^{67}Ga scan showed more extensive disease than the CT scan. The use of ^{67}Ga scan for staging resulted in increasing the assigned stage of all 4 patients. Figure 1 shows CT and ^{67}Ga scans for one representative case in whom ^{67}Ga scan resulted in upstaging. This patient



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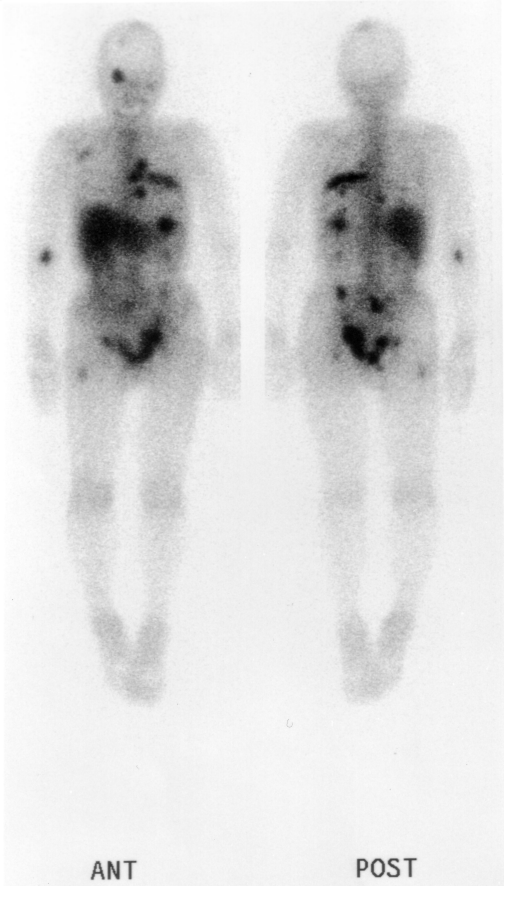

B

Fig. 1 CT and ^{67}Ga scintigraphic scans in a 79-year-old female with non-Hodgkin's lymphoma. CT using contrast medium demonstrates a homogeneous mass shadow at the right orbit (A). The whole body ^{67}Ga image demonstrates very intense accumulation in the right orbit with additional skull, rib, vertebra, pelvic bone, right femur and spleen involvement. Right elbow is injection site (B). On the basis of ^{67}Ga scintigraphy, this patient was upstaged from stage I E to stage IV.

underwent biopsy for non-Hodgkin's lymphoma of the right orbit.

The results changed from positive to negative accumulation in 20 (95.2%) of the 21 patients who had ^{67}Ga scintigraphy to assess their response to treatment. These 20 patients showed a good clinical course and were alive 6 months after completion of treatment. The remaining one patient did not achieve remission and died 6 months after ^{67}Ga scintigraphy.

DISCUSSION

In the present study, the sensitivity on ^{67}Ga scan in the extranodal lymphomas (other than those of skin and urinary bladder and low grade lymphoma) was similar to the incidence of that in nodal non-Hodgkin's lymphoma (75–90%), and confirms that the ^{67}Ga scan is able to detect extranodal lymphoma with approximately the same sensitivity as nodal lymphoma. However, further studies in a large number of patients with skin and urinary bladder lymphomas should be evaluated because the number of these patients was small. The ^{67}Ga scan has been reported to be more likely to be significantly positive in cases of high and intermediate grade lymphoma than low grade one among nodal lymphoma.[15] These results are similar to the results of the present study. Thallium-201 has been shown to provide more information in low grade nodal non-Hodgkin's lymphoma and may be more helpful in such cases.[16]

The relative advantage of ^{67}Ga imaging is its ability to survey the whole body at one scanning. Because lymphoma may involve both the nodal and extranodal lymph nodes, whole body ^{67}Ga scintigraphy provides an additional clinical advantage. The present study has shown ^{67}Ga scintigraphy to provide additional information in staging of 4 patients (6%). These results are in agreement with a previous report.[17] Hussain et al.[17] reported that ^{67}Ga scintigraphy affected staging or treatment in seven patients (8%). This was due to the detection on ^{67}Ga scintigraphy of disease sites distant from the primary extranodal lymphoma that were not detected by other means.

The sensitivity of ^{67}Ga scan is not only dependent on cell type but also on the size and location of the lesion. The minimal detectable lesion diameter with ^{67}Ga planar scan is usually above 1 cm. The site of lymphoma also affects the sensitivity of ^{67}Ga scan. In the present study, ^{67}Ga imaging showed a high sensitivity for the detection of breast, chest wall and esophagus lymphoma. On the other hand, the sensitivity for the stomach lymphoma is 64.3%. Kataoka et al.[18] reported that 23 of 25 lesions (92%) were detected by ^{67}Ga scintigraphy in patients with lymphoma of gastrointestinal tract. This is in contrast with our results. One of the reasons may be the difference in the tumor size between the two studies. It is often difficult to differentiate possible disease sites from physiologic accumulation in the abdomen with ^{67}Ga planar scintigraphy and, therefore, the sensitivity and specificity of this technique are low for abdominal tumors. Use of SPECT increases the sensitivity of ^{67}Ga imaging and localizes tumor sites better than does planar scintigraphy.[19] In the present study, if SPECT was not performed, pancreatic lymphoma could not have been clearly detected. Thus, SPECT appears to be necessary to detect smaller and deeper lesions. Recently, a multi-head gamma camera system for SPECT has been introduced and applied widely in nuclear medicine examinations and this could further improve the detection of small lesions.

In the present study, we used 111–148 MBq ^{67}Ga-citrate, which is less than 296 MBq used in a series of studies by Front et al.[14,19,20] in patients with malignant lymphoma. We used 111–148 MBq because this is the standard dose administered to adult patients in Japan. Higher doses of ^{67}Ga may improve image quality and, consequently, the diagnostic accuracy of ^{67}Ga scintigraphy for evaluating extranodal malignant lymphoma. Nakayama et al.,[21] however, reported that ^{67}Ga scans obtained in 46 non-Hodgkin's lymphoma patients with only 74 MBq ^{67}Ga-citrate were similar to those using a higher dose. Thus, we also consider that the relativity lower dose of 111–148 MBq used in the present study and routinely administered in our department, was sufficient for detecting high rate activity in extranodal malignant lymphoma.

The value of ^{67}Ga scintigraphy for monitoring the response to treatment in lymphoma involving the lymph nodes and other soft tissue is well documented.[20] Negative ^{67}Ga findings at the end of treatment indicate a good response and outcome, regardless of the presence or absence of a residual mass on CT.[22] Persistent ^{67}Ga uptake at the end of treatment indicates the presence of active disease. ^{67}Ga scintigraphy provides a means for early diagnosis of recurrence,[4] and some studies have shown that ^{67}Ga scintigraphy performed early during treatment is a good predictor of prognosis and outcome.[5,23] In the present study, ^{67}Ga scan was performed in 21 patients to assess the therapeutic response. In 20 of these patients the abnormal ^{67}Ga accumulation disappeared in comparison with pre-treatment ^{67}Ga study. All of these patients with negative ^{67}Ga accumulation were alive at 6 month follow-up. On the other hand, one patient in whom abnormal ^{67}Ga accumulation did not disappear showed a close correlation between the findings of ^{67}Ga imaging and the therapeutic effects. This patient died 6 months after ^{67}Ga scintigraphy. Documented ^{67}Ga avidity in extranodal lymphoma lesions at diagnosis is the basis for further assessment of treatment response during and after therapy. It must be remembered that ^{67}Ga scintigraphy after treatment can be performed in only ^{67}Ga avid tumors. Bartold et al.[24] also reported that the argument for performing ^{67}Ga scintigraphy before treatment is that it provides reference data for the optimal interpretation of post-

therapy scan. The role of ^{67}Ga scintigraphy in the prediction of therapy outcome and as a screening test following therapy should be further evaluated in a larger number of extranodal lymphoma patients.

Irrespective of the pathology, ^{67}Ga scintigraphy is more sensitive for lesions above the diaphragm than those in the abdominal and pelvic regions.[25] PET using ^{18}F-FDG is highly sensitive both below and above the diaphragm and for both superficial and deeply located lesions, and appears to be an accurate and non-invasive method for the detection of bone marrow involvement. As a consequence, PET findings can alter staging of the disease in up to 16% of patients with Hodgkin's disease or non-Hodgkin's lymphoma.[12] Advantages of PET scan over ^{67}Ga imaging include better resolution and, to a lesser extent, more favorable dosimetry. However, many practical problems are associated with the use of PET in clinical imaging, such as high cost and lack of availability. Little information is available on the comparison of PET and ^{67}Ga in the assessment of patients with extranodal lymphoma. Further well-designed studies are required to determine the appropriate role of these imaging modalities in the proper management of patients with extranodal lymphoma.

CONCLUSION

^{67}Ga scintigraphy did not show positive accumulation in patients with skin and urinary bladder lymphomas. Furthermore, low-grade and small extranodal lymphomas had a low rate of ^{67}Ga scintigraphy positivity. However, it was helpful to confirm the diagnosis and to evaluate the therapeutic effect in most patients with extranodal malignant lymphoma.

REFERENCES

1. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. *Cancer* 1972; 29: 252–260.
2. Edwards CL, Hayes RL. Tumor scanning with ^{67}Ga citrate. *J Nucl Med* 1969; 10: 103–105.
3. Kostakoglu L, Yeh SD, Portlock C, Heelan R, Yao TJ, Niedzwiecki D, et al. Validation of gallium-67-citrate single-photon emission computed tomography in biopsy-confirmed residual Hodgkin's disease in the mediastinum. *J Nucl Med* 1992; 33: 345–350.
4. Front D, Bar-Shalom R, Epelbaum R, Haim N, Ben-Arush MW, Ben-Shahar M, et al. Early detection of lymphoma recurrence with gallium-67 scintigraphy. *J Nucl Med* 1993; 34: 2101–2104.
5. Front D, Bar-Shalom R, Mor M, Haim N, Epelbaum R, Frenkel A, et al. Hodgkin disease: prediction of outcome with ^{67}Ga scintigraphy after one cycle of chemotherapy. *Radiology* 1999; 210: 487–491.
6. Delcambre C, Reman O, Henry-Amar M, Peny AM, Macro M, Cheze S, et al. Clinical relevance of gallium-67 scintigraphy in lymphoma before and after the therapy. *Eur J Nucl Med* 2000; 27: 176–184.
7. Nishiyama Y, Yamamoto Y, Ono Y, Satoh K, Ohkawa M, Yamauchi A, et al. Visualization of esophageal non-Hodgkin's lymphoma with Ga-67 scintigraphy. *Ann Nucl Med* 1999; 13: 419–421.
8. Yamamoto Y, Nishiyama Y, Kawakita K, Toyama Y, Ohkawa M, Tanabe M. Malignant lymphoma of the central nervous system with delayed increased accumulation on I-123 IMP SPECT. *Clin Nucl Med* 2001; 26: 105–108.
9. Nishiyama Y, Yamamoto Y, Fukunaga K, Satoh K, Ohkawa M. Ga-67 scintigraphy in patients with breast lymphoma. *Clin Nucl Med* 2002; 27: 101–104.
10. Moog F, Bangerter M, Diederichs CG, Guhlmann A, Kotzerke J, Merkle E, et al. Lymphoma: role of whole-body 2-deoxy-2-(F-18)-fluoro-D-glucose (FDG) PET in nodal staging. *Radiology* 1997; 203: 795–800.
11. Buchmann I, Reinhardt M, Elsner K, Bunjes D, Altehoefer C, Finke J, et al. 2-(Fluorine-18) fluoro-2-deoxy-D-glucose positron emission tomography in the detection and staging of malignant lymphoma. *Cancer* 2001; 91: 889–899.
12. Kostakoglu L, Leonard JP, Kuji I, Coleman M, Vallabhajosula S, Goldsmith SJ. Comparison of fluorine-18 fluorodeoxyglucose positron emission tomography and Ga-67 scintigraphy in evaluation of lymphoma. *Cancer* 2002; 94: 879–888.
13. National Cancer Institute sponsored study of classification of non-Hodgkin's lymphomas. Summary and description of a working formation for clinical usage. *Cancer* 1982; 49: 2112–2135.
14. Front D, Israel O. The role of Ga-67 scintigraphy in evaluating the results of therapy of lymphoma patients. *Semin Nucl Med* 1995; 25: 60–71.
15. Kostakoglu L, Goldsmith SJ. Fluorine-18 fluorodeoxyglucose positron emission tomography in the staging and follow-up of lymphoma: is it time to shift gears? *Eur J Nucl Med* 2000; 27: 1564–1578.
16. Waxman AD, Eller D, Ashook G, Remanna L, Brachman M, Heifeltz L, et al. Comparison of gallium-67 citrate and thallium-201 scintigraphy in peripheral and intrathoracic lymphoma. *J Nucl Med* 1996; 37: 46–50.
17. Hussain R, Christie D, Gebski V, Barton MB, Gruenewald SM. The role of the gallium scan in primary extranodal lymphoma. *J Nucl Med* 1998; 39: 95–98.
18. Kataoka M, Kawamura M, Tsuda T, Itoh H, Komatsu A, Tanada S, et al. The role of gallium-67 imaging in non-Hodgkin's lymphoma of the gastrointestinal tract. *Eur J Nucl Med* 1990; 17: 142–147.
19. Front D, Israel O, Epelbaum R, Ben Haim S, Sapir EE, Jerushalmi J, et al. Ga-67 SPECT before and after treatment of lymphoma. *Radiology* 1990; 175: 515–519.
20. Front D, Ben-Haim S, Israel O, Epelbaum R, Haim N, Even-Sapir E, et al. Lymphoma: predictive value of Ga-67 scintigraphy after treatment. *Radiology* 1992; 182: 359–361.
21. Nakayama M, Sakahara H, Minowa Y, Sasai K, Ishigaki T, Saga T, et al. Value of low-dose gallium-67 imaging in detection of non-Hodgkin's lymphoma recurrence. *Radiat Med* 1997; 15: 79–83.
22. Israel O, Mekel M, Bar-Shalom R, Epelbaum R, Hermony N, Haim N, et al. Bone lymphoma: ^{67}Ga scintigraphy and CT for prediction of outcome after treatment. *J Nucl Med* 2002; 43: 1295–1303.
23. Front D, Bar-Shalom R, Mor M, Haim N, Epelbaum R,

Frenkel A, et al. Aggressive non-Hodgkin lymphoma: early prediction of outcome with ^{67}Ga scintigraphy. *Radiology* 2000; 214: 253–257.
24. Bartold SP, Donohoe KJ, Fletcher JW, Haynie TP, Henkin RE, Silberstein EB, et al. Procedure guideline for gallium scintigraphy in the evaluation of malignant disease. *J Nucl Med* 1997; 38: 990–994.
25. Stomper PC, Choleweinsky SP, Park J, Bakshi SP, Barcos MP. Abdominal staging of thoracic Hodgkin disease; CT-lymphangiography-Ga-67 scanning correlation. *Radiology* 1993; 187: 381–386.