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The prognostic value of conventional imaging tools to determine how patients with hodgkin lymphoma will respond to treatment

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ABSTRACT

Introduction: This systematic review studies the prognostic value of two conventional imaging tools, sestamibi and gallium scans, for predicting how patients with Hodgkin lymphoma will respond to treatment.
Methods: The PubMed database was searched for English-language articles that contained the following search terms: (Hodgkin AND [mibi OR sestamibi OR gallium OR spect] AND response). All articles that were identified during this search were included in the study, regardless of date published. The inclusion criteria were as follows: articles that described studies that were limited to Hodgkin patients and that reported the predictive value of conventional imaging tools. Articles about other types of lymphoma and/or those that focused on the diagnostic and staging accuracy of mibi and gallium scans were excluded.
Result: In total, 14 articles were retrieved. Of these, the majority met the inclusion criteria of the systematic review with the exception of two, which were limited to an examination of the reliability of performing sestamibi scans to predict the response to treatment. All remaining 12 articles considered both the sestamibi scans and the gallium scintigraphy.
The results of the systematic review indicate that positive gallium scan results can be proposed as a poor prognostic factor that is associated with partial or full recurrence of Hodgkin disease, a reduction in overall survival rate, and progression-free survival compared with patients with a negative scan.
Discussion: Both sestamibi and gallium scans revealed high sensitivity and specificity in predicting the response to treatment including complete remission, partial remission, and recurrence of the disease.
Conclusion:These imaging tools can appropriately assess how Hodgkin patients will respond to chemotherapy. As such, clinicians can use these tools to devise appropriate treatment strategies.

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Introduction

Radiation therapy and chemotherapy alone or in combination have been proposed as the main treatment approaches for patients at an early or advanced stage of Hodgkin lymphoma. In some cases, these therapies have resulted in complete response and prolonged survival (1).

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Evaluating how a patient may respond to treatment is important, but difficult, especially in patients with residual radiological abnormalities. Imaging techniques represent a significant and effective method by which therapeutic strategies for patients with Hodgkin disease can be managed.

Gallium-67 citrate uptake is transferrin receptor-dependent, and it can be used to reveal an active metabolic process and also to predict disease activity in residual mediastinal mass following therapy. This tracer is not absorbed in fibrotic or necrotic tissue; however, it is absorbed by avid and viable HL (Hodgkin Lymphoma) tissue. As such, 67Ga is proposed as an indicator of tumor viability (2).

Whole-body 67gallium (67Ga) scintigraphy is a valuable and sensitive imaging tool, not only for the diagnostic purposes of lymphoma, but also for evaluating the response to treatment including complete remission, partial remission, and recurrence of the disease. Although the 67Ga scintigraphy procedure is able to predict how patients with Hodgkin lymphoma may respond to treatment, physiological accumulation of gallium in the intestine limits the efficacy of this imaging tool in abdominal parts of the body (3). As such, a gallium scan is more sensitive for lesions that are located above the diaphragm than it is for abdominal and pelvic diseases (4).

The 99mTc-MIBI (99mTc-methoxyisobutylisonitrile) imaging procedure is recognized to have a prognostic factor regarding response to chemotherapy in various types of malignancies including lung cancer (5), malignant lesions (6), Hodgkin's and non-Hodgkin's lymphoma, etc. (7-9). The effectiveness and utility of 99mTc-MIBI scintigraphy has also been investigated in some types of lymphomas. However, these studies have typically employed different methodologies and obtained different results.

This systematic review studied the results described in various articles that focused on the prognostic value of conventional imaging techniques that employed Ga67 and 99mTc-MIBI.

Methods

According to the purpose of this study, the PubMed database was searched using the following keyword strategy: (Hodgkin AND [mibi OR sestamibi OR gallium OR spect] AND response). The inclusion criteria were all articles that studied the prognostic value and sensitivity of gallium scintigraphy and Technetium-99m-sestamibi in predicting response treatment and disease outcome. According to the included studies, response to treatment was reported as complete remission, partial remission, and relapse of the disease. The procedures can be performed before initiating the therapy, during the treatment, or after the treatment. Only English-language articles were included in this systematic review. No limitations regarding date of publication were applied. The exclusion criteria were all the non-English articles that studied patients with lymphomas except Hodgkin and any articles that investigated the diagnostic sensitivity or staging accuracy of the mentioned imaging strategies.

Results

Information regarding the process by which the articles were selected and the number of articles that were included in the final assessment are provided in the flowchart presented in Figure 1.

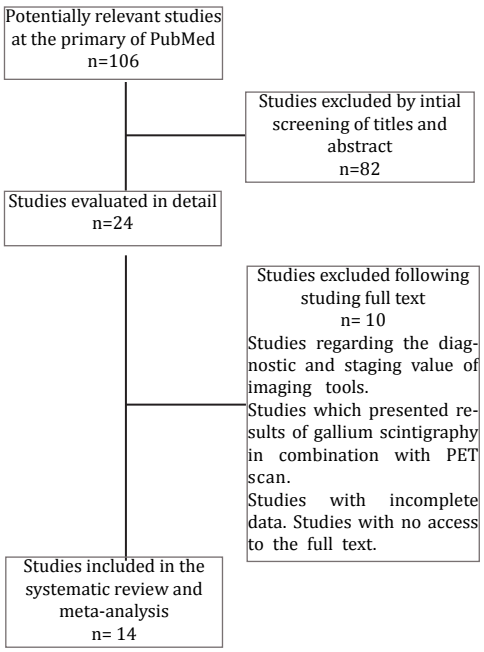

Figure 1. Show the strategy of including related articles in the systematic review

According to the search strategy, inclusion, and exclusion criteria, a total of 14 articles were initially included in this systematic review. Of these, the majority met the inclusion criteria of the systematic review with the exception of two, which were limited to an examination of the reliability of performing sestamibi scans to predict the response to treatment. All remaining 12 considered both the sestamibi scans and the gallium scintigraphy.

Supradiaphragmatic lesions were evaluated in all the articles that studied the prognostic value of mibi. Regarding 99mTc-mibi, due to physiological tracer accumulation in intra-abdominal organs, abdominal SPECT was not performed in patients with both supradiaphragmatic and subdiaphragmatic lesions.

Lymphomas were classified according to the

Table 1. Quality control results of the included studies.

NO	Author Year Reference	Was the sample of patients assembled at a common point in the course of their disease?	Follow up duration	Were outcome criteria either objective or applied in a 'blind' fashion?	Outcome reported
1	Spyridonidis 2013 (10)	Yes	45.5 ± 23.5 M	Yes	Sensitivity/ specificity
2	Kapucu 1997 (11)	Yes	1-2 yrs	No	Sensitivity
3	Herman 2007 (12)	Yes	6-54 M	NO	Sensitivity/Specificity/PFS
4	Ng 2005 (13)	Yes	Median 64 M	No	OS/PFS
5	Castellani 2003 (14)	Yes	Follow up 13-168 M	Yes	Relapse rate
6	Brenot-Rossi 2001 (3)	Yes	28-124 yrs	NR	Sensitivity/Specificity
7	Nikpoor 2000 (15)	Yes	Average follow up:4.5 yrs	Yes	Relapse rate
8	Delcambre 2000 (16)	Yes	Mean 31 M	NO	CR rate
9	Ionescu 2000 (17)	Yes	Median 36 M	-	
10	Front 1999 (18)	Yes	12-120 M	No	CR/PR rate
11	Setoain 1997 (19)	Yes	Follow up:6-20 M	No	Sensitivity/Specificity
12	Hagemeister 1994 (20)	Yes	NA	No	FFP
13	King 1994 (21)		Median 28 M	Not available	-
14	Anderson 1983 (22)	Yes	10-24 M	NR	Recurrence rate

DFS: disease free survival, PFS: progression free survival, OS: overall survival, CR: complete remission, PR: partial remission, R:relapse, FFP:freedom from progression, M: month

World Health Organization classification.

Quality control of the included studies was performed based on the criteria published by the Oxford Centre for Evidence-based Medicine and are summarized in Table 1. Data are presented as the sensitivity and specificity of the imaging tools in terms of ability to predict a patient's response to treatment and recurrence of the lymphoma. Data regarding the author, reference number, patients' characteristics, tracer dose, outcome (sensitivity and specificity of imaging procedure in predicting response to first-line therapy and final outcome which can be lymphoma-specific survival, overall survival, disease or progression-free survival) are summarized in Table 2.

Discussion

Predicting the possibility of disease recurrence and response to treatment will be beneficial for the improvement of the therapeutical interventions that are administered to patients with lymphoma.

99mTc-MIBI SPECT

According to the extracted data, 99mTc-MIBI imaging is a putative imaging approach for providing prognostic information about chemotherapy response and guiding therapeutic decisions following baseline evaluation of patients with lymphoma. In the study performed by Kapucu et al., the results obtained by conducting 99mTc-sestamibi scintigraphy in patients with complete response

Table 2. Summarized information of the included studies regarding the prognostic value of sestamibi and gallium scans in Hodgkin patients.

	Author Year Reference	Patients	Dose	Therapy response
Mibi	Spyridonidis 2013 (10)	N:47 (16 HL, 31 NHL) 32 M,15 F Age range: 17-87 yrs Follow up: 45.5 T 23.5 Months	740 MBq (20 mCi)	Sensitivity%-specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 48.4 -72.7
	Kapucu 1997 (11)	N:24 (16 HL, 8 NHL) 13M,11F Age range: 1-17yrs	5-10 mCi (185-370 MBq) 99mTcsestamibi Uptake≥ 2+: +	+ 99mTc-sestamibi OR (CR):14/16 with HL 3/8 with NHL Sensitivity%:70%
Ga^{67}	Herman 2007 (12)	N:30 17M,13F Age:19-50 yrs	320–360MBq	Sensitivity for predicting relapse: 50% Specificity for predicting relapse: 88.5% 2-yr PFS Ga-: 92.8% Ga+:60.5%
	Ng 2005 (13)	N:175 93M,82F Age: 9–71yrs	-	5-year OS (Ga-: 97%) (Ga+:53%) 5-year PFS (Ga-: 93%) (Ga+:38%)
	Castellani 2003 (14)	N:71 Age range 4-17 yrs	37-111 MBq	R rate in post therapy Ga+:50% (8/16) R rate in post therapy Ga-:10.6%(6/55) M rate in post therapy Ga+:31.2%(5/16) M rate in post therapy Ga-:3.6%(2/55)
	Brenot-Rossi 2001 (3)	N:74 67Ga negative, N:61 67Ga positive, N:13 41 M, 33 F Age range:14-62 yrs	222 MBq (6 mCi).	Response to therapy in Ga- CR:16.4% PR:83.6 Relapse in Ga- CR:20% PR:19.6% Response to therapy in Ga+ CR:0.07% PR:92.3% Relapse in Ga+ CR:100% PR:84% Sensitivity for predicting relapse: 58% Specificity for predicting relapse: 96% DFS: (Ga-: 80.3%), (Ga+:15.4%) OS: (Ga-: 91.8%), (Ga+:61.5%)
	Nikpoor 2000 (15)	N:85 38M,47F Age range 16-76 yrs	10 mCi (370 MBq)	Clinial remission/ R(death)/R(alive) Normal Ga (38): 34/0/4 Borderline Ga (45): 40/1/4 Abnormal Ga (2): 0/2/0
	Delcambre 2000 (16)	N:62(52 HD, 10 NHL) 39 M, 23 F Median follow up: 32 months	185–220 MBq	Ga+: 17/22 (77%) in remission Ga-: 1/9 (11%) in remission
	Ionescu 2000 (17)	N:53	Not available	-FFP (Ga+:19%), (Ga-:86%) OS (Ga+:25%), (Ga-:91%)
	Front 1999 (18)	N:98 50M,48F Age range:5-76 yrs	Adults: 8 mCi (296 MBq/Kg) Children: 75 mCi (2.77 MBqKg)	treatment failure after one treatment cycle Ga +: 4/7 Ga-:2/24 CR after one treatment cycle Ga +: 3/7 Ga-:22/24 Mid-treatment failure Ga +: 1/5 Ga-:14/78 Mid-treatment CR Ga +: 4/5 Ga-:64/78
	Setoain 1997 (19)	N:53(37 HL, 16 NHL) 36M,17F Age range:16-76 yrs Recurrence, N::28 Residual, N:25	370 MBq 67Ga-citrate	Overall sensitivity (%) and specificity(%): 90%(19/21)-92%(35/38) Recurrence: Sensitivity of 88 Specificity of 100 Accuracy of 92 Residual mass (response to treatment) Sensitivity of 100 Specificity of 86 Accuracy of 88
	Hagemeister 1994 (20)	N:46	8 to 10 mCi	3-year FFP Ga+:70% Ga-:100%
	King 1994 (21)	N:33	Not available	RFS (Ga+:8%), (Ga-:75%)
	Anderson 1983 (22)	N: 21 HL(43 scans)	7 to 10 mCi	Active disease Ga +: 29/29 Ga-:1/14

N: number. M: male, F: female, HL: Hodgkin, NHL: non-hodgkin, T/B: tumor-to-background, Early (20 minutes), Late (120 minutes), Washout: 2 hours, Ga -: 67Ga negative group, Ga +: 67Ga positive group, DFS: disease free survival, PFS: progression free survival, OS: overall survival, CR: complete remission, PR: partial remission, PD: progressive disease, FFP:freedom from progression, Follow up: NA, R:relapse, M: mortality, normal: no residual mediastinum–hilar (M-H) uptake, borderline: M–H residual uptake was less than that of sternum or spine, abnormal: residual M–H residual uptake was more than that of the sternum or spine, RFS: recurrence free survival

to treatment were significantly different than those obtained from 99mTc-sestamibi scintigraphy in patients with partial or no response to chemotherapy (23). According to the researchers' findings, regardless of the lymphoma type, all the cases with positive 99mTc-sestamibi imaging (lesions positively detected) responded positively to treatment; however, those with negative 99mTc-sestamibi (the inability to demonstrate lymphoma lesions) showed partial or no response to treatment (23). It is possible that overexpression or increased functioning of Pgp molecules and subsequently outward transportation of sestamibi molecules from tumor cells could induce the negative 99mTc-sestamibi results in patients with poor response to therapy (23).

The existing studies also indicate that Technetium-99m-sestamibi accumulation is greater in HD lesions than it is in NHL. The study performed by Spyridonidis et al. considered scintigraphic indices (early T/B, late T/B, and two hours washout) and found that late T/B ratio was associated with a higher prognostic value over clinical prognostic factors including age, lymphoma type, Ann Arbor stage, and lactate dehydrogenase levels. Delayed 99mTc-mibi uptake is proposed as independent and incremental prognostic factor of time to disease progression and lymphoma-related death in comparison to the other scintigraphic indices and clinical prognostic factors (10).

From the review of the existing literature, it can be concluded that prescreening with 99mTc-sestamibi has prognostic value regarding the response to treatment and clinical outcome of patients with HL.

Gallium^{67}

A small number of residual cells can be sufficient for the recurrence for HL, although developing enough cell masses to cause a relapse will take a long time. Delayed relapse is one characteristic of the HL; as such, the study by Castellani et al. examined almost 15 years of follow-up for the included patients (14). Gallium-67 citrate is known as a viability factor that is absorbed only by cancer tissue and not by fibrotic or necrotic tissues. Ga scintigraphy procedure is based on the absorption of this ferric ion analogue by tumor cells; especially the white blood cells. It is assumed that the absorption of Ga67 is related to the cells' proliferation rate; more aggressive tumors exhibit a higher rate of absorption. However, well-differentiated tumor types have a lower absorption rate (24). Several advantages have been associated with the use of a ^{67}Ga scintigraphy as a tumor viability factor such as the ability to identify tumor recurrence by scanning the whole body and the ability to distinguish between active tumor and fibrosis tissue. This entails that ^{67}Ga scintigraphy can be employed to discriminate between patients who are at a low or high risk of malignancy relapse (3,12,25).

Ga ^{67} absorption change following treatment is associated with absence or the presence of tumor cells and can evaluate the possibility of lymphoma relapse and the biological aggressiveness of the malignancy, which can change the subsequent optimum treatments (16).

It can be suggested that a sufficient dose of the 370 MBq and high-quality SPECT have prognostic value in terms of malignancy recurrence.

According to a report by Front et al., performing Ga scintigraphy after one cycle of treatment has prognostic value regarding the evaluation of the clinical outcome of the patients and can separate patients with favorable outcome from those with unfavorable outcomes (18). Front et al. were unable to achieve favorable results by performing Ga scintigraphy at the mid-treatment point to predict failure of response to treatment (recurrence or partial remission). As such, they concluded that early Ga scintigraphy following one cycle of treatment could predict the treatment outcome and early change in subsequent therapeutic strategies (18). Eventually, they suggested that the application of lower doses of chemotherapy for patients with negative Ga results after one cycle of treatment would not negatively affect the patients' survival rates.

Setoain et al. found that ^{67}Ga showed higher sensitivity and specificity for the detection of malignancy relapse compared with the computed tomography procedure. They suggested that 67Ga-scintigraphy should be routinely performed as part of the management of patients with HL (19). They also found that patients with Ga+ results had a higher mortality rate than those with Ga- cases (relative risk of 5.2). Similar results have also been confirmed in other studies, despite differences in the disease stage at first screening, types of applied treatment strategy, technique and interpretation of the gallium images, types of applied treatment subsequent positive gallium scan, and the follow-up duration. In all the included studies, HL patients with positive gallium scan were associated with poor clinical prognosis (13,14,17,20,22). As such, the gallium scan results should directly impact any decisions that are made regarding further treatment strategies due to the extent to which they can predict post-treatment risk of recurrence.

Generally, in the case of patients treated following initial presentations and those with recurrent disease, performing ^{67}Ga scintigraphy has prognostic value for evaluating response to therapy

and for the early detection of relapse. The absorption rate of Ga can be regarded as an indicator of treatment efficacy. In the study of Castellani et al. (14), this procedure accurately predicted the clinical outcome in 97% of the included patients.

One study reported the normal, borderline, and abnormal uptake of Ga through using sternum and spinal uptake as a reference that reflected bone marrow localization of Ga-67 (15). The researchers suggested that that mild M-H (Mediastinum-Hillar) uptake with intensity less than that of the sternum or spine may indicate post-treatment fibrosis rather than residual tumor. They concluded that the quantitative evaluation of Ga-67 tracer in the M-H area following treatment is greatly sensitive in differentiating between active tumor and benign uptake. Normal and borderline Ga-67 uptake in the M-H area can be associated with a low likelihood of recurrence and indicates better prognosis (15).

Due to the high specificity of 67Ga scintigraphy, the application of high doses of chemotherapy consolidation would be favorable and advantageous for patients with ^{67}Ga+ results. On the other hand, this procedure has low sensitivity in predicting the disease recurrence in patients with negative post-treatment Ga scan, due to incomplete remission or inability to detect the residual malignant tissue. As such, by performing Ga scintigraphy following one cycle of treatment, the accuracy of any prediction may increase. However, performing the Ga scintigraphy mid-treatment or after the completion of the chemotherapy may be associated with lower sensitivity in predicting the outcome.

Conclusion

^{99}mTc-MIBI imaging can be proposed as prognostic criterion for chemotherapy response; however, further studies are needed to confirm these results.

According to the existing literature, the advantageous of performing ^{67}Ga scintigraphy for monitoring HL is apparent. This aging tool can appropriately assess the response to chemotherapy and, therefore, play an important role in treatment decisions. A positive gallium scan can be proposed as a poor prognostic factor, which is associated with decreased OS, FFTF, and PFS compared with patients with a negative gallium scan.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Sacks P, Jacobs P, Gale D, et al. Combination chemotherapy in the treatment of advanced Hodgkin's disease. S Afr Med J. 1973;47:903-907.
2. Nejmeddine F, Raphael M, Martin A, et al. 67Ga scintigraphy in B-cell non-Hodgkin's lymphoma: correlation of 67Ga uptake with histology and transferrin receptor expression. J Nucl Med. 1999;40:40-45.
3. Brenot-Rossi I, Bouabdallah R, Di Stefano D, et al. Hodgkin's disease: prognostic role of gallium scintigraphy after chemotherapy. Eur J Nucl Med. 2001;28:1482-1488.
4. Karimjee S, Brada M, Husband J, et al. A comparison of gallium-67 single photon emission computed tomography and computed tomography in mediastinal Hodgkin's disease. Eur J Cancer. 1992;28:1856-1857.
5. Mohan HK, Miles KA. Cost-effectiveness of 99mTc-sestamibi in predicting response to chemotherapy in patients with lung cancer: systematic review and meta-analysis. J Nucl Med. 2009;50:376-381.
6. Dimitrakopoulou-Strauss A, Strauss LG, Goldschmidt H, et al. Evaluation of tumour metabolism and multidrug resistance in patients with treated malignant lymphomas. Eur J Nucl Med. 1995;22:434-442.
7. Kao CH, Tsai SC, Wang JJ, et al. Evaluation of chemotherapy response using technetium-99M-sestamibi scintigraphy in untreated adult malignant lymphomas and comparison with other prognosis factors: a preliminary report. Int J Cancer. 2001;95:228-231.
8. Lazarowski A, Dupont J, Fernández J, et al. 99mTechnetium-SESTAMIBI uptake in malignant lymphomas. Correlation with chemotherapy response. Lymphat Res Biol. 2006;4:23-28.
9. Ohta M, Isobe K, Kuyama J, et al. Clinical role of Tc-99m-MIBI scintigraphy in non-Hodgkin's lymphoma. Oncol Rep. 2001;8:841-845.
10. Spyridonidis TJ, Matsouka P, Symeonidis A, et al. (99m)Tc sestamibi as a prognostic factor of response to first-line therapy and outcome in patients with malignant lymphoma. Clin Nucl Med. 2013;38:847-854.
11. Kapucu LO, Akyüz C, Vural G, et al. Evaluation of therapy response in children with untreated malignant lymphomas using technetium-99m-sestamibi. J Nucl Med. 1997;38:243-247.
12. Turner DA, Pinsky SM, Gottschalk A, et al. The Use of 67Ga Scanning in the Staging of Hodgkin's Disease. Radiology. 1972;104:97-101.
13. Ng AK, Bernardo MV, Silver B, et al. Mid- and post-ABVD gallium scanning predicts for recurrence in early-stage Hodgkin's disease. Int J Radiat Oncol Biol Phys. 2005;61:175-184.
14. Castellani MR, Cefalo G, Terenziani M, et al. Gallium scan in adolescents and children with Hodgkin's disease (HD). Treatment response assessment and prognostic value. Q J Nucl Med. 2003;47:22-30
15. Nikpoor N, Aliabadi P, Diaz L, et al. Long-term follow-up of residual mediastinal-hilar Ga-67 uptake after treatment for Hodgkin's and non-Hodgkin's lymphomas: what degree of Ga-67 uptake is significant? Clin Nucl Med. 2000;25:959-962.
16. Delcambre C, Reman O, Henry-Amar M, et al. Clinical relevance of gallium-67 scintigraphy in lymphoma before and after therapy. Eur J Nucl Med. 2000;27:176-184.
17. Ionescu I, Brice P, Simon D, et al. Restaging with gallium scan identifies chemosensitive patients and predicts survival of poor-prognosis mediastinal Hodgkin's disease patients. Med Oncol. 2000;17:127-134.
18. Front D, Bar-Shalom R, Mor M, et al. Hodgkin disease: prediction of outcome with 67Ga scintigraphy after one cycle of chemotherapy. Radiology. 1999;210:487-491.
19. Setoain FJ, Pons F, Herranz R, et al. 67Ga scintigraphy for the evaluation of recurrences and residual masses in patients with lymphoma. Nucl Med Commun. 1997;18:405-411.
20. Hagemeister FB, Purugganan R, Podoloff DA, et al. The gallium scan predicts relapse in patients with Hodgkin's disease treated with combined modality therapy. Ann Oncol. 1994;5

Suppl 2:59-63.
21. King SC, Reiman RJ, Prosnitz LR. Prognostic importance of restaging gallium scans following induction chemotherapy for advanced Hodgkin's disease. J Clin Oncol. 1994;12:306-311.
22. Anderson KC, Leonard RC, Canellos GP, et al. High-dose gallium imaging in lymphoma. Am J Med. 1983;75:327-331.
23. Kapucu LO, Akyuz C, Vural G, et al. Evaluation of therapy response in children with untreated malignant lymphomas using technetium-99m-sestamibi. J Nucl Med. 1997;38:243-7.
24. Draisma A, Maffioli L, Gasparini M, et al. Gallium-67 as a tumor-seeking agent in lymphomas--a review. Tumori. 1998;84:434-441.
25. Edwards CL, Hayes RL. Scanning malignant neoplasms with gallium 67. JAMA. 1970;212:1182-1191.