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Clinical Significance of Non-Hodgkin's Lymphoma with an Irregular、Non-Contrast-Enhanced Area
不規則な非-造影剤増強領域を持つ非ホジキンリンパ腫の臨床的意義

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Clinical Significance of Non-Hodgkin's Lymphoma with an Irregular, Non–Contrast-Enhanced Area

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Background: An irregular, non–contrast-enhanced area shown on postcontrast computed tomography (CT) or postcontrast magnetic resonance imaging (MRI) in cases of non-Hodgkin's lymphoma (NHL) may indicate that the primary tumor has a high degree of malignancy. This study was planned to determine whether this indicated a poor prognosis.

Methods: Fifty-six patients with NHL (32 males and 24 females) underwent diagnostic imaging; the internal characteristics of the primary lesion were evaluated retrospectively by 2 radiologists. Postcontrast CT with 2 mL/kg of contrast medium was performed in 46 cases during the equilibrium phase, and postcontrast MRI was also performed in 10 cases by the spin echo method following an 0.1 mmol/kg intravenous injection of gadopentetate.

Results: Ten (17.8%) of the 56 cases with NHL showed an irregular non–contrast-enhanced area. The 5-year survival rate for cases with homogeneous enhancement was 77.5%, while the actuarial survival rate at 44 months for cases with an irregular non–contrast-enhanced area was 25.4% ($P < 0.005$). From the results of multivariate analysis using Cox's regression model for 11 factors (internal characteristics, sex, age, clinical stage, primary site, size, lactic dehydrogenase value, systemic symptoms, cell marker, histopathologic criteria, and therapy), symptoms ($P = 0.0001$) and internal characteristics ($P = 0.0164$) were selected as the variants affecting the prognosis. No correlations were found between internal characteristics and other variants.

Conclusion: Contrast CT or MRI should be evaluated before treatment, as the presence of an irregular non–contrast-enhanced area indicates a poor prognosis.

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Key words: non-Hodgkin's lymphoma, CT, MRI, necrosis, non–contrast-enhanced area, prognosis

INTRODUCTION

Several reports have shown that lymphomas with an irregular, non–contrast-enhanced area inside the lesion have a higher malignancy and a poorer prognosis than lymphomas that show homogeneous contrast enhancement on computed tomography (CT) or magnetic resonance imaging (MRI).[1,2] However, there has been insufficient investigation concerning the correlation to other background factors such as clinical stage, lesion size, and primary site, and concerning the independence of non–contrast-enhanced areas as a prognostic factor. In this paper, we report the results of multivariate analysis performed to determine the clinical significance of image findings showing an irregular, non–contrast-enhanced area inside a lesion that has been diagnosed as non-Hodgkin's lymphoma (NHL).

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PATIENTS AND METHODS

NHL was histopathologically diagnosed in 56 patients, who had CT and MRI scans before treatment. Patient characteristics are shown in Table 1. The patients were 32 males and 24 females, with an age distribution of 10 to 84 years (mean, 58.6). The distribution of clinical stages, according to the Ann Arbor classification,[3] were stage I, 19 cases; stage II, 19 cases; stage III, 8 cases; and stage IV, 10 cases. The histopathologic criteria were based on the working formulation.

There were 4 methods of treatment: radiotherapy alone, radiotherapy followed by chemotherapy, chemotherapy followed by radiotherapy, and chemotherapy alone. Patients in the radiotherapy alone group and radiotherapy followed by chemotherapy group were irradiated locally at a dose of 60 gray/30 fractions/6 to 7

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weeks (60 Gy/30 f/6 to 7 wk), generally with cobalt 60 gamma rays. Subsequent chemotherapy consisted of 3 to 5 courses of mainly vincristine, cyclophosphamide, procarbazine, and prednisone (VEPP) or cyclophosphamide, vincristine, and prednisone treatment. In the groups in which chemotherapy was performed first or only chemotherapy was performed, the treatment consisted of 2 to 7 courses of bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone; or prednisone, methotrexate, calcium leucovorin, doxorubicin, cyclophosphamide, and etoposide with cytaBOM (proMACE-cytaBOM: prednisone, calcium leucovorin, doxorubicin, cyclophosphamide, cytarabine, pepleomycin, vincristine, and methotrexate). In these groups, the dose of radiation, given after chemotherapy, was 40 Gy/20 f/5 wk.

Diagnostic imaging was performed on all patients before treatment, and the internal characteristics of the primary lesion on CT and MRI images were evaluated retrospectively by 2 radiology specialists. CT images were used for the evaluation in 46 cases, and MRI images were used in 10 cases in which no CT scan had been performed. For the CT imaging, 2 mL/kg of nonionic contrast medium was used, and the CT was performed during the equilibrium phase. A 1.5 T superconducting machine was used for MRI, which was also performed in the equilibrium phase by the spin echo method at Tl-weighted imaging (TR 500 ms/TE 15 ms) following an 0.1 mmol/kg intravenous injection of gadopentetate. A T2-weighted imaging was not used as a rule for evaluation reference.

Statistical Analysis

Statistical significance was determined by the chi-square test (including a correction factor) and Fisher's direct probability method. We used the Kaplan-Meier method for calculating the survival rate, the log-rank test for assessing significant differences, and Cox's multiregression life table for multivariate analysis. A difference of $P < 0.05$ was considered to be statistically significant.

RESULTS

A CT scan showing a homogeneous contrast enhancement inside a lesion and an MRI scan showing an irregular, non–contrast-enhanced area inside a lesion are depicted in Figs. 1 and 2, respectively. Ten of the 56 patients (17.9%) in this study showed an irregular, non–contrast-enhanced area inside the lesion.

As for the relation between the presence or absence of a non–contrast-enhanced area and a complete remission after treatment, the results showed that a complete remission was not obtained in 8.7% (4/46) of the patients with a homogeneous contrast area. In patients with a non–contrast-enhanced area, the percentage of

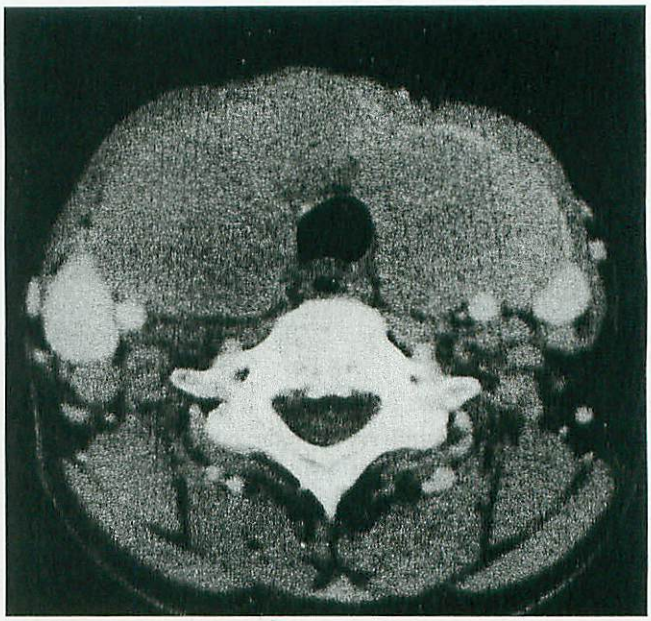

Fig. 1. Postcontrast computed tomography (transverse imaging) showing diffuse swollen thyroid gland with homogeneous contrast enhancement inside the lesion (non-Hodgkin's lymphoma of the thyroid gland, diffuse, large cell, B cell, 55-year-old woman).

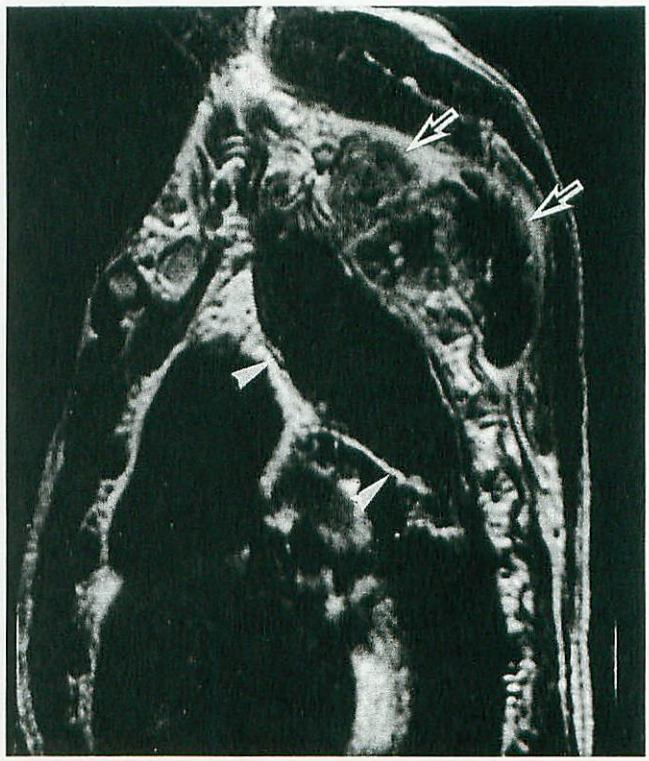

Fig. 2. Postcontrast magnetic resonance image (T1-weighted sagittal imaging) showing a large tumor (arrows) with an irregular non–contrast-enhanced area inside the lesion (non-Hodgkin's lymphoma, pyothorax-associated lymphoma, diffuse large cell, B cell or null type, 64-year-old man). The tumor proliferated adjacent to the cyst-like wall of chronic pyothorax (arrowheads), posteriorly invaded into the back muscle.

unsuccessful remissions was much higher at 30% (3/10 cases), although this difference was not statistically significant ($0.05 < P < 0.1$). The recurrence rate was 35.7% in patients with a homogeneous contrast area (15/42 patients with a complete remission), and a much higher 57.1% in patients with a non–contrast-enhanced area (4/7 patients with a complete remission). However, a significant difference was not found. A significant difference ($P < 0.005$), however, was found in the survival rates between the 2 groups. The 5-year survival rate of patients with a homogeneous contrast area was 77.5%, whereas the survival rate of patients with a non–contrast-enhanced area at 44 months was only 25.4% (Fig. 3).

Figure 4 shows the relapse-free survival rates. A significant difference ($P < 0.05$) in the relapse-free survival rates was seen between the 2 groups: 63.2% of the patients with a homogeneous contrast area survived for 5 years versus 0% at 34 months for the patients with a non–contrast-enhanced area.

Multivariate analysis was done for the following 11 factors: sex, age, clinical stage, presence or absence of symptoms, primary site, size of the lesion, lactic dehydrogenase value, histopathologic criteria, character of cell surface, method of treatment, and the internal characteristics of the lesion (ie, presence/absence of a non–contrast-enhanced area). The results showed that the presence or absence of symptoms and the internal characteristics of the lesion had significant effects on the prognosis ($P = 0.0001$ and $P = 0.0164$, respectively) (Table 2). A clear correlation was not found between the internal characteristics of the lesion and the other factors (Table 1).

DISCUSSION

Malignant lymphomas are less necrotic than carcinomas and produce lesions with a high, uniform cell density.[4] Image findings also reflect these features of malignant lymphomas; the lymphomas are often depicted on CT or MRI images as a homogeneous lesion with a weak contrast effect.[4] However, an irregular, non–contrast-enhanced area is also sometimes seen inside the lesion. The frequency of such an observation was reported by Amano et al.[2] to be 8.6%, and Rehn et al.[1] reported the frequency to be 10% in low-grade malignant cases of NHL and 63% in high-grade malignant cases. Hopper et al.[5] reported that in mediastinal Hodgkin's disease, necrosis was seen in 21% of the lymph nodes. In the present investigation, a non–contrast-enhanced area was seen in 17.8% of the cases. A simple comparison to the results of past studies, however, is thought to be difficult because of differences in the patients and background factors.

The irregular, non–contrast-enhanced area in images has been attributed to an outgrowth of necrotic region and fibrous connective tissue.[4] However, according to Rehn et al.,[1] the frequency of heterogeneous contrast enhancement is very high in cases where there is necrosis inside the lesion, but only 27% in cases with no necrosis. Also, heterogeneous contrast enhancement is seen in 30% of cases with no fibrous tissue or only a slight degree of fibrous tissue. In this study, although we could not compare the histopathologic and image findings for all patients, it seemed that cases that showed a non–contrast-enhanced area had relatively extensive necrosis. The peculiarities of the disease are given as one reason why it is difficult to compare histopathologic and image findings.

Chemotherapy, radiotherapy, or a combination of both are the usual methods for treating malignant lymphomas. Therefore, surgical resection is rarely chosen as the method of treatment. The final diagnosis is generally based on the results of a biopsy, which is easy to perform if the primary lesion is in a region such as the

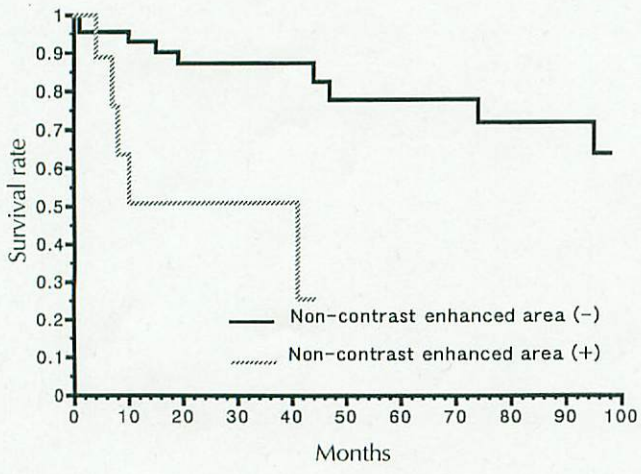

Fig. 3. Actuarial survival curve of 56 patients with non-Hodgkin's lymphoma, according to internal characteristics of the lesion. (−), absent; (+), present.

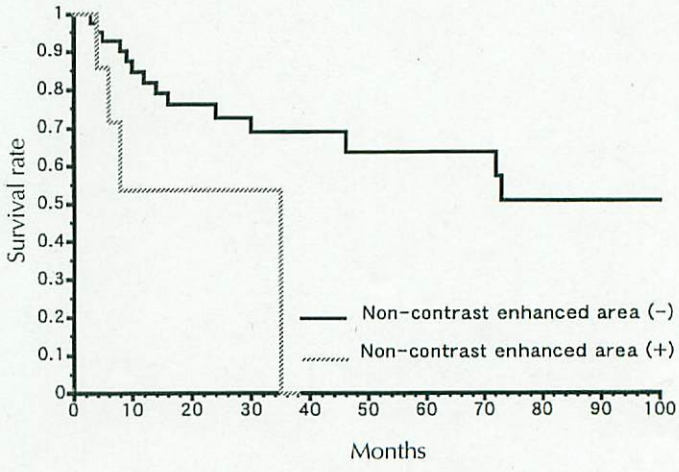

Fig. 4. Relapse-free survival curve of 49 patients with non-Hodgkin's lymphoma, according to internal characteristics of the lesion. (−), absent; (+), present.

Table 1. Characteristics of 56 patients with non-Hodgkin's lymphoma.

Variable	NCEA (+)	NCEA (–)	NCEA (+) / NCEA (+) + NCEA (–)	*P* value
Sex				
Male	8	24	25.0%	0.1022
Female	2	22	8.3%	
Age (y)				
< 65	7	34	17.1%	0.5392
≥ 65	3	12	20.2%	
Stage				
I	2	17	10.5%	0.6126
II	5	14	26.3%	
III	1	7	12.5%	
IV	2	8	20.2%	
Symptoms				
Present	7	41	14.6%	0.1428
Absent	3	5	37.5%	
Primary site				
Waldeyer's ring	3	13	18.8%	0.8623
Lymph node	2	13	13.3%	
Extranodal	5	20	20.0%	
LDH				
WNL	5	29	14.7%	0.1670
Elevation	5	17	22.7%	
Pathology				
Low	1	4	20.0%	0.9892
Intermediate	8	37	17.8%	
High	1	5	16.7%	
Cell marker				
B cell	7	24	22.6%	0.1710
T cell	0	8	0.0%	
Lesion size[a]				
< 7 cm	5	35	12.5%	0.1610
≥ 7 cm	5	11	31.3%	
Therapy				
XRT alone	1	6	14.3%	0.7341
XRT → chemo	0	3	0.0%	
Chemo → XRT	4	21	16.0%	
Chemo alone	5	16	23.8%	

NCEA, non–contrast-enhanced area; XRT, x-ray therapy; chemo, chemotherapy; (+), present; (–), absent; LDH, lactic dehydrogenase; WNL, within normal limits; XRT, radiation therapy. [a]maximum diameter.

Table 2. Summary of the fit proportional hazard model for prognosis in 56 patients with non-Hodgkin's lymphoma.

Variable	Beta	Chi-square	*P* value	*R*
Symptom[a]	3.23863	15.96	0.0001	0.386
Internal characteristics[b]	1.54444	5.76	0.0164	0.200

[a]presence vs. absence of symptoms; [b]presence of non–contrast-enhanced area vs. absence of non–contrast-enhanced area.

palatine tonsil or body surface organs, but more difficult to perform when the primary lesion exists in the deep thoracal or abdominal regions. However, even if a biopsy sample is taken from the primary lesion, resection of the whole primary focus is rarely performed, and in many cases, a sample of sufficient size for comparison cannot be obtained. Thus, an accumulation of data from further case studies is needed to do a more detailed comparison of the internal characteristics of the lesion and the histopathologic findings.

The purpose of the present investigation was to determine whether an accurate prognosis can be made based on the image findings. If information is available to determine the prognosis before commencing treatment for malignant lymphomas, this information would be very useful for choosing the appropriate method of treatment. From their investigation of NHL cases including high- and low-grade malignant groups, Rehn et al.[1] found that the prognosis was poor in cases that showed a non–contrast-enhanced area inside the lesion compared with those that did not, although there was no significant difference between cases with and without a non–contrast-enhanced area in the high-grade malignant group. Hopper et al.[5] reported that there was no significant difference in the survival rates or remission periods between patients with mediastinal Hodgkin's disease with a non–contrast-enhanced area and those without a non–contrast-enhanced area. In this study, although a clear difference was not found in the frequencies of a non–contrast-enhanced area according to the histopathologic degree of malignancy, there was a significant difference in survival rates depending on the presence or absence of a non–contrast-enhanced area. In addition, the results of multivariate analysis showed the independence of the internal characteristics (presence or absence of a non–contrast-enhanced area) as a factor in determining the prognosis.

These differences in the prognosis may be explained by (1) the possibility of high-grade malignancy in the lesion itself that is not indicated by the histopathologic type; (2) the possibility that malignancy increases arithmetically or synergistically in association with other background factors; or (3) the possibility that the non–contrast-enhanced area may not respond sufficiently to treatment.

Regarding the malignancy of the lesion itself, Som[6] reported that lymph stream obstruction and necrosis occur easily in lymph nodes, which have a fast rate of lesion proliferation. This seems to indicate that lymph nodes with an irregular, non–contrast-enhanced area are more malignant.

Previously, we also investigated the factors that affect the prognosis of NHL, using univariate and multivariate analysis.[7–9] The results showed that the main factors affecting the prognosis are age, size of the lesion, site of first occurrence, histopathologic criteria, clinical stage, lactic dehydrogenase value, presence or absence of symptoms, and method of treatment. It was thought that some of these factors were correlated with the internal characteristics of the lesion. However, the results of this investigation failed to show any clear correlation between any of the background factors. Rehn et al.[1] and Amano et al.[2] reported that they could not find any correlation between the size of the lymph node and the internal characteristics of the lesion. Although it has been reported that many lymphomas show a non–contrast-enhanced area in cases of mediastinal Hodgkin's disease,[10,11] the few studies so far conducted on NHL (including the present study) failed to show any such tendency.[1,2] However, it has been shown that images of "pyothorax-associated lymphomas,"[12] including the 1 case in this study, show extensive degeneration and necrosis in the lesion, and the prognosis is extremely poor.[13] Only a small degree of necrosis[4] and a good prognosis[14] have been reported for cases of thyroid malignant lymphomas, which is interesting from the point of view of the relationship among organ sites, image findings, and prognosis. It has also been reported that in malignant lymphomas with the primary site in the brain, the frequency of a non–contrast-enhanced area inside the lesion is high in cases complicated by AIDS,[15] whereas a non–contrast-enhanced region can be seen in only 13% to16.6%[15,16] of non-AIDS cases. Thus, complications are also thought to affect the differences in the frequency of a non–contrast-enhanced area.

As for the response to treatment, it has been reported that in cases of lesions with a non–contrast-enhanced area the main response is the non–contrast-enhanced area itself[2]; therefore, the existence of a non–contrast-enhanced region does not in itself necessarily indicate resistance to treatment. Oliver et al.,[17] who investigated changes in the CT image after treatment, reported that after treatment the lesion showed no tendency to grow, and there was a good prognosis in cases where the internal characteristics of the lesion had changed due to necrosis or fat substitution. However, further investigation is needed to clarify points such as how the image changes after treatment in the case of lesions with a non–contrast-enhanced area, whether there are any histopathologic differences in the non–contrast-enhanced areas, and what is the relationship to treatment and prognosis.

In conclusion, a total of 17.8% of the NHL cases investigated in this study showed an irregular, non–contrast-enhanced area inside the primary lesion, and the prognosis for these cases was poor compared with the prognosis for cases that showed homogeneous contrast enhancement on CT or MRI images. The results of multivariate analysis also indicated that the presence of a non–contrast-enhanced area inside the lesion is an important factor affecting the prognosis. Thus, determining the characteristics inside the lesion by CT or MRI imaging may be important for determining an accurate prognosis.

REFERENCES

1. Rehn SM, Nyman RS, Glimelius BLG, Hagberg HE, Sundstrom JC. Non-Hodgkin's lymphoma: predicting prognostic grade with MR imaging. Radiology 1990;176:249–253.
2. Amano Y, Takahama Y, Hayashi H, Katagiri K, Ichikawa T, Takagi R, Miyashita T, Horiuchi J, Kumazaki T. CT and MRI findings of malignant lymphoma with non-enhanced areas. Jpn J Clin Radiol 1993;38:821–824.
3. Proceedings of the Symposium on Contemporary Issues in Hodgkin's Disease: biology, staging, and treatment. Cancer Treat Res 1982;66:601–1067.
4. Machara Y, Hashida I, Nakayama Y, Furuta M, Sakaino K. Malignant lymphoma in cervical region. Jpn J Diag Imaging 1991;11:896–905.
5. Hopper KD, Dichl LF, Cole BA, Lynch JC, Meilstrup JW, McCauslin MA. The significance of necrotic mediastinal lymph nodes on CT in patients with newly diagnosed Hodgkin's disease. AJR 1990;155:267–270.
6. Som PM. Lymph nodes of the neck. Radiology 1987;165:593–600.
7. Saitoh Y, Yoshida H, Takashio T, Shuke N, Yamada T, Yoshikawa D, Kawaguchi K, Tohyama S, Mineta M, Aburano T, Ishikawa Y, Satoh J, Kikuchi Y. The evaluation of serum deoxythymidine kinase (s-TK) activity in malignant lymphoma. J Jpn Soc Cancer Ther 1995;30:781–790.
8. Saitoh Y, Kikuchi Y, Hayasaka K, Amoh K, Fujita M, Uekita Y, Nishino S. Effective evaluation of combination chemotherapy in stage I–II of non-Hodgkin's lymphoma—a comparison of treatment with multivariate analysis. Jpn J Cancer Clin 1989;35:804–810.
9. Saitoh Y, Yoshikawa D, Yamada T, Takashio T, Hayasaka K, Mineta M, Aburano T, Kikuchi Y. Non-Hodgkin's lymphoma of stage I and II in elderly patients: a retrospective study in comparison with younger patients. Nippon Acta Radiologica 1995;55:576–581.
10. Negendank WG, Al-Katib AM, Karanes C, Smith MR. Lymphomas: MR imaging contrast characteristics with clinical-pathologic correlations. Radiology 1990;177:209–216.
11. Nyman RS, Rehn SM, Glimelius BLG, Hagberg HE, Hemmingsson AL, Sundstrom CJ. Residual mediastinal masses in Hodgkin's disease: prediction of size with MR imaging. Radiology 1989;170:435–440.
12. Iuchi K, Ichimiya A, Akashi A, Mizuta T, Lee YE, Tada H, Mori T, Sawamura K, Lee YS, Furuse K, Yamamoto S, Aozasa K. Non-Hodgkin's lymphoma of the pleural cavity developing from long standing pyothorax. Cancer 1987;60:1771–1775.
13. Daido K, Arita K, Doi M, Nambu S, Asaoku H, Nagashima A, Sasaki Y, Wadasaki K, Mori M. A clinical study on intrathoracic malignant lymphoma with chronic tuberculous pyothorax. J Jpn Assoc Thorac Surg (Nippon Kyobu Geka Gakkai Zasshi) 1991;29:866–872.
14. Li CC, Mohri N, Sakamoto A, Machinami R. A pathological study of primary malignant lymphomas of the thyroid. Jpn J Cancer Clin 1990;36:2111–2118.
15. Lee YY, Bruner JM, Tassel PV, Libshitz HI. Primary central nervous system lymphoma: CT and pathologic correlation. AJR 1986;147:747–752.
16. Tan EC, Wakabayashi S, Kanai H, Nagai H. Ring-enhanced primary intracranial malignant lymphoma—report of two cases. Neurol Med Chir 1991;31:214–218.
17. Oliver TW, Bernardino ME, Sones PJ. Monitoring the response of lymphoma patients to therapy: correlation of abdominal CT findings with clinical course and histologic cell type. Radiology 1983;149:219–224.