Necessity of routine computed tomography after the end of the lymphoma treatment

I.Kriachok., K.Filonenko, A.Martynchyk, E. Kushchevyy

National Cancer Institute, Kyiv

Summary: After the end of lymphoma treatment clinicians have a difficult choice: is it necessary to provide any follow-up, in which way and how often. The most complicated choice is a question about computed tomography because of its high cost and radiation dose. This article contain summer of literature on the subject of routine computed tomography in the follow-up period and our own data on frequency of relapse detection with or without routine computed tomography and its influence on the future results of the treatment.

Key words: lymphoma, examination, computed tomography, relapse, radiographic methods

Modern level of the lymphoma therapy permits to reach good results with high level of response and long-term remissions. This brings new challenges to the clinicians, includingin which way and how often to provide screening after the end of the treatment.

Necessity of the screening oneself probably isn't a question. Different lymphoma types often require. The risk of second malignancies and other toxic effects of chemoradiotherapy is known also. This brings a need of timely detection and treatment of these disorders.

The article mainly covers the role of computed tomography (CT) as routine diagnostic procedure after the end of the lymphoma treatment. Though this method has high informational value, that permit to suspect relapse, quite high radiation dose and high cost of the method are its main shortcomings.

The discussion between clinicians about routine CT necessity was started since CT was introduced into the routine practice of the lymphoma diagnosis and treatment. For the analysis of the available data we performed the search of the publications in the electronic database PubMed. We used key words: computed tomography, lymphoma, follow-up. 1170 publications in the period from 1977 to 2011 were found. Only 28 publications from 1986 to 2011 were used as the most corresponded to the topic of the article.

The start to modern recommendations at the diagnosis and follow-up of lymphoma patients was given with recommendations of Cotswolds, 1989 [1]. There were indicated, that patients hould be examined every 3 months during first 2 years, every 4 months during 3rd year, every 6 months till 5 years, then – annually. Authors recommended to perform radiographic tests depend on primary tumor localization. More precise recommendations weren't indicated.

CT could be the most useful for relapse detection among other radiographic methods by the opinion of some investigators. Researches form 80-90th XX century provided the idea about importance of routine CT as a relapse detection method in patients with Hodgkin's disease (HD) and Non-Hodgkin's lymphomas (NHL). Garribba AP et al., 1990publishedresultsofinvestigationof the role of routine CT in the staging and follow-up of the HD patients. 120 patients were included into the study. CT was more informative then X-ray of chest, especially in patients in the follow-up period.[2]

The same data were published by Rezvani Letal, 1986 in the publication of the results of study of Burkitt's Lymphoma's diagnosis, response evaluation and relapse detection. [3]

Contrary data were received later. The study of Radford J A et al showed, that 81% of relapses in HD patients were revealed clinically. [4]

Dry veretal published results of the relapse detection in patients with HD. 187 patients who were under observation in the Toronto Sunny brook Regional Cancer Centre during the period of 1990-1999 were included into retrospective analysis. The data were available in 107 patients. [5]

Patients' visits were performede very 3 months during first two years, every 6 months during 3^{rd}-5^{th} years, then – annually. Observation included questioning, physical examination, X-ray of chest, complete blood count (CBC). Other radiographic tests were performed by physician's opinion. Median of observation was 38 months (1-120 months).

Relapse was suspected in 109 cases in 68 patients. In42% of cases- based on patient's complaints and questioning, in 26 % - results of patient's examination, in 28 % - results of radiographic tests, in 4 % - laboratory data. Relapse was confirmed in 22 patients. Among these patients 10 had relapse suspected based on complaints and questioning, 4 — results of patient's examination, 6 — results of radiographic tests. Among last 6 patients X-ray was performed in 4 patients, CT – in 2 patients. Among 25 false-positive results of relapse detection 7 conclusions were made based on X-ray, 12 – CT, 5- gallium scanning, 1 – ultrasound.

Thereby, majority of relapses were detected based on patient's complaints. Radiographic tests revealed a quarter of relapses, but it takes one half of the cost of all investigations. CT revealed 9% of relapses, but its cost takes 29% of all investigations. In addition routine CT more often gives false-positive results of relapse suspicion. Thereby authors insist upon exclusion of routine CT from algorithm of patient's observation after the end of the HD's treatment.

Guadagnolo et al constructed the model of financial propriety of annual routine CT scanning in patients after the end of HD treatment. They revealed that 92 % of relapses were detected by disease symptoms. They revealed that CT scanning in such regimen, besides other routine charges, costs from 149,900 to 291,500 USA dollars per patient's year of life. Also, extremely negative influence of false-positive results of relapse detection on patient's quality of life was exposed. [6]

Results of retrospective population study published in 2010 by Hodgson D. et al showed similar data. Routine CT scanning after the end of HD therapy lead to the start of second-line therapy very rare. On the contrary screening of secondary malignancies (e.g., early screening of breast cancer) was performed not enough. This investigation included the data of all patients who were under the observation in the Clinic of Ontario University from 1992 to 2002. Observation period was 1-15 years. Every patient visited physician 4 times per year at the average and had at least one radiographic test. Totally 5,352 CT scanning were performed in all patients. 66% of patients underwent CT during 2-5th years after the end of the treatment, 44,4% - during 6-9th years and 32,7 % - during 10-15th years. CT was performed more often in

patients, who received the treatment in the University Clinic then in patients, who were treated not in scientific hospitals. About 40 % of patients didn't undergo cancer screening despite of the indications. Relapse treatment was initiated only in 125 patients after the 5,352 of investigations during 2-5th years after the end of lymphoma therapy. In the conclusion authors summarized that it's quite possible to avoid CT scanning in patients with HD. All patients' and physicians' efforts should be directed to the detection of other diseases. [7]

In the article of Ng A, Constine LS et al., dedicated to the observation of the patients after the end of HD therapy, had affirmed that the modern data don't leave any place to routine radiographic tests during first five years. Only for female patients who received radiotherapy on the mediastinum before 35 years old annual breast cancer screening is recommended. [8]

Liedtke et al described the data of 108 patients with relapse of aggressive NHL treated with ICE chemotherapy followed by high-dose chemotherapy with autologous hematopoietic stem cell transplantation (HDCT + AHSCT). Relapse was suspected based on patients' complaints or physical examination in 80% of patients, and based on radiographic methods – in 20% of patients. Authors revealed that patients from second group had positive prognosis and tendency to bit higher 5-year survival, but not significant (54% vs 43%). [9]

In the study of Nakamura K, et al the ways of relapse detection were described in 101 patient with local stages of NHL (mostly head and neck localization). Relapse was detected in 31 patients. In 17 patients (56.4%) it was suspected based on symptoms of the disease, in 10 (32.2%) — based on clinical examination. CT revealed relapse in 3

patients, gallium scanning – in 2 patients, increase of lactatedehydrohenase (LDH) – in 2 patients. In 72.7% of patients with symptomatic relapse tumor spread corresponded to stage III-IV of the disease. At the same time in 70.6% of patients with a symptomatic relapse tumor spread corresponded to stage I-II of the disease.[10]

Elis A, et al analyzed the data of 30 patients with relapse of aggressive NHL. Intensive algorithm of observation after the successful first-line treatment was used in this group of patients. It included thick graphic of visits to the physician, laboratory tests (CBC, LDH level measurement) and routine CT. 25 (83%) of relapses were detected during clinical examination of patients: 5 (17%) – during laboratory or radiographic tests. Relapses localized mostly on the place of primary tumor. Thereby, investigators summarized, that the mos tappropriate schedule of observation should include frequent visits to the physician and clinical examination of patients.[11]

In the Guppy et al study only 5,7% of relapses in patients with DLBCL were suspected after the routine CT performing in a symptomatic patients. [12]

J. O. Armitage and F. R. Loberiza analyzed publications devoted to the regular examination of patients with aggressive lymphomas after the end of the therapy. They also concluded that this method should be avoided as a routine test. [13]

Choi J Y et al conducted the study devoted to the role of CT in relapse detection in patients with indolent lymphomas, e.g. MALT-lymphoma of stomach. 7 relapses were detected in 122 patients with H. Pylori positive lymphoma of stomach. All of them were limited by the stomach area and were verified by endoscopy. Investigators made the conclusion that it isn’t useful to performed CT in this group of patients.[14]

Authors of another study analyzed data in relapse detectionin 125 patients with relapse of HD or aggressive NHL diagnosed in 1993-2008. Relapse was detected one and more months after the end of first-line treatment. 62% of relapses were suspected based on clinical data, especially in patients with aggressive NHL or extranodal involvement ($p < 0.05$). Survival rates weren't higher among the group of patients, where relapse was revealed with CT scanning. [15]

There sults of prospective study of Thompson CA, et al were published on Annual ASCO Meeting 2013 (American Society of Clinical Oncology). The aim of the study was to determine the most effective strategy of patients' observation after the end of the lymphoma treatment. Observation tactic was chosen by physicians. Data of 537 among 644 patients included to the study in 2002-2009 were used. Relapse was detected in 109 patients. In 62% of cases patients visited their physician earlier planned visit due to presence of abnormalities. 68% of them had disease symptoms, in 42% pathologic signs were found during physical examination, 55% had LDH elevation, 87% - had one or more of these findings. In 38 patients relapse was revealed on planned visit. In 26 patients relapse was detected by clinical signs, in 12- during scanning. In 4 patients among 12 positive PET (positrone emission tomography) scanning was positive at the end of first-line treatment. Thereby routine scanning revealed only 8 relapses (1.5%). As a result authors make conclusion about low informative value of routine scanning for DLBCL relapse detection [16].

On the other hand, by the opinion of Hutchings M., routine CT and PET/CT still important for high risk group patients. The author recommends tostop CT scanning

after two years after the end of treatment even in this group, as 90% of relapses occur during this period. Radiographic tests are senseless in a symptomatic patients with indolent NHL, because relapse treatment should be started only in case of symptom presence.[16]

Australian researches Beyan C e tal. analyzed the influence on the risk of secondary malignancies of CT radiation dose during staging, treatment and follow-up in 15 patients with HD. Median of radiation dose during 14.5 months drawn 85.19 mSv and 161.08 mSv by the data of National Radiological Protection Board and Biological Effects of Ionizing Radiation VII report, respectively. Cumulated dose after all radiographic tests increased the risk of secondary malignancies 1:1000 in 8,5-16 times according Biological Effects of Ionizing Radiation VII report. The same dose had natural radiation background during 35-70 years. This study showed that radiation dose received bypatients during all radiographic tests since HD diagnos is enough for secondary malignancy appearing. That's why they proposed to reassess the algorithm of observation of patients with HD after the end of treatment. [17]

Current guidelines in lymphoma diagnosis and treatment in Ukraine and foreign countries partially regulate radiographic tests performing. Unfortunately sometimes they contradict each other or are incomplete.

One of foreign guidelines is "Clinical Practice Guidelines for the Diagnosis and Management of Lymphoma" elaborated by The Cancer Council Australia/Australian

Cancer Network and approved by the National Health and Medical Research Council on 159th session on December, 8th 2005 [18]

The Guideline content the data about necessity of patient observation every 2-6 months depend on the lymphoma type. The observation includes clinical examination, CBC and biochemistry. Other diagnostic procedures in lymphoma patients finished their treatment, including radiographic, should be recommended only in case if indication are present. The guideline contains the data of 709 patients with I and II stage HD. Among them 69% of relapses were detected by clinical data. [19] Furthermore, the authors emphasize that observation schedule after the end of the treatment is very individual and not regulated.

Other foreign guidelines contain the similar data. The observational procedures recommended by ESMO after the end of HD treatment embrace patients' complaints collection, physical examination, CBC, erythrocyte sedimentation rate (ESR) and biochemistry once per 3 months during first year after the end of the treatment, every 6 months before 4th year, then annually. Oncologic screening is required due to risk of secondary malignancies. CT and other radiographic tests should be performed only in case of indications. [20] NCCN Clinical practice guidelines in diagnosis and treatment of HD published in 2013 onthe contrary regulate the schedule of radiographic tests in the follow-up period. The recommendations are to perform X-ray or CT of chest every 6-12 months during first 2-3 years, then – in case of need. CT of abdomen or pelvic should be performed every 6-12 months during first 2-3.

Later radiographic tests are used only for screening of late toxic effects of chemotherapy. [21]

ESMO Guidelines consensus conference on malignant lymphoma 2011 has similar recommendations in clinical and laboratory examination for different types of NHL – every 3-6 months during first two years after the treatment end, then – annually. [22, 23] Minimal radiographic tests are recommended every 6 months during first two years after the treatment end, then – annually for follicular lymphoma (FL). [24] Authors recommend to minimize radiographic tests application in patients with MALT-lymphoma and cutaneous lymphoma. [25, 26]. The recommendation describes routine radiographic tests after the end of therapy of DLBCL. Mainly it's present by CT performed on 6, 12 and 24 month after the treatment end. Still thee fficacy of this regimen wasn't evident. [27]

NCCN Clinical practice guidelines in diagnosis and treatment of NHL published in 2013 indicate the need of clinical and laboratory testing every 3-6 months during first 5 years, then annually or by indications. CT is recommended for FL, marginal zone lymphoma and DLBCL not frequently then every 6 months during first two years, then – annually or by indications. CT doesn't indicate as diagnostic procedure for patients with MALT-lymphoma after the end of therapy. In this case every 3 months endoscopy should be performed. Similar is the situation with mantle cell lymphoma and peripheral T-cell lymphomas. Clinical examination is recommended in the observation period. [28]

Though the hope pined on routine CT in follow-up period in patients with different lymphoma types weren't justified in more recent publications. The authors mainly

believe that principal ways of relapse detection are patient's complaints and physical examination. 62 to 91% of relapses were suspected based on these data. Routine CT in the follow-up period doesn't enable to suspect relapse reliably. It also has high costandradiationdose. The smallest diagnostic value it has in indolent lymphoma patients. Contrary wise there is the opinion of usefulness of routine CT in patients with aggressive lymphomas. However, authors recommend to limit such observation with two year period. The influence of routine CT on patients' survival wasn't reveal. All these data were reproduced in modern guidelines in lymphoma diagnosis and treatment. Nevertheless authors of publications underline that there is no enough investigations for final decision.

Through the absence of precise algorithm of observation after the end of lymphoma treatment and single opinion of necessity of routine CT we performed the analysis of group of patients, who were treated in oncohematology department of National Cancer Institute in 2008-2011.

Materials and Methods

58 patients diagnosed with NHL (36 patients) and HD (22 patients) in the period from 1995 to 2011 and had relapse of the disease were included. Among them were 30 males and 28 females in age from 21 to 78 years old, median - 49 years. Relapse was detected later then 3 months after the end of the induction treatment. The assessment of the ways of relapse detection was performed. Relapses were detected clinically (based on patient's complaints, anamnestic data or clinical examination) or

by regular CT results. Patient's observation had next schedule: regular visits to the physician every 3-12 months and CT conduction every 6-12 months depend on the period of observation.

Clinical and hematological data, frequency of relapse detection clinically or by regular CT, 5-year over all survival (OS), median OS in both groups were assessed. Also analysis of potential causes of revealed differences in both groups was planned.

Results

Significantly frequently relapse was detected clinically — in 36 patients (62 %). There were no difference in frequency in the ways of relapse detection depend on histological type of lymphomas: in 14 among 22 patients with HD (64 %) and in 22 among 36 patients with NHL (61 %), $p>0.05$. These data correspond to the submitted above data.

Both groups of relapse detection clinically and by routine CT were similar by principal characteristics (age, gender, histological type, stage at the moment of diagnosis, B-symptoms) (see Table 1).

Table 1. Principalclinical and hematological characteristics at the diagnosis of lymphoma in the groups of patients in which relapse was detected clinically or by regular CT

Characteristic	Group of patients in which relapse was detected clinically	Group of patients in which relapse was detected by regular	p>0.05

		CT	
Gender: Male/female	19/17	11/11	
Median age	51	49	
B-symptoms	21 from 36 (58 %)	10 from 22 (46 %)	
Histological type: HD/NHL	14/22	8/14	
Stage at the diagnosis: early/advanced	17/19 (47 % / 53 %)	10/12 (45 % / 55 %)	

The analysis of the frequency of relapse detection among histological subtypes of NHL showed that in patients with aggressive subtypes (DLBCL, mantle cell lymphoma, peripheral T-cell lymphoma) relapses were detected clinically in 15 among 23 patients (65 %), in patients with indolent subtypes - in 7 among 12 patients (58 %), $p>0.05$.

Observation period in the whole group of patients was 9-196 months since the moment of the diagnosis, median was 34 months. In the group of HD patient observation period was 9-196 months, median 46 months, in the group of NHL patients – 14-89 months, median 31 months.

Relapses were detected in the whole group of patients in the period of 4-190 months, median 13 months, in the group of HD – in the period of 4-190 months, median 12 months and in the group of NHL patients – in the period of 4-69 months, median 27 months.

Significant difference was revealed after analysis of patients' survival. 5-year OS was higher in thegroup with relapses detected by regular CT 81.8±9.2% compare to 58.6±9.9% in the group with relapses detected clinically ($p<0.05$). Median survival wasn't reach in both groups (see Figure).

Results of 5-year OS in our study contradict published data, which report absence of significant difference in OS depend on the way of relapse detection.

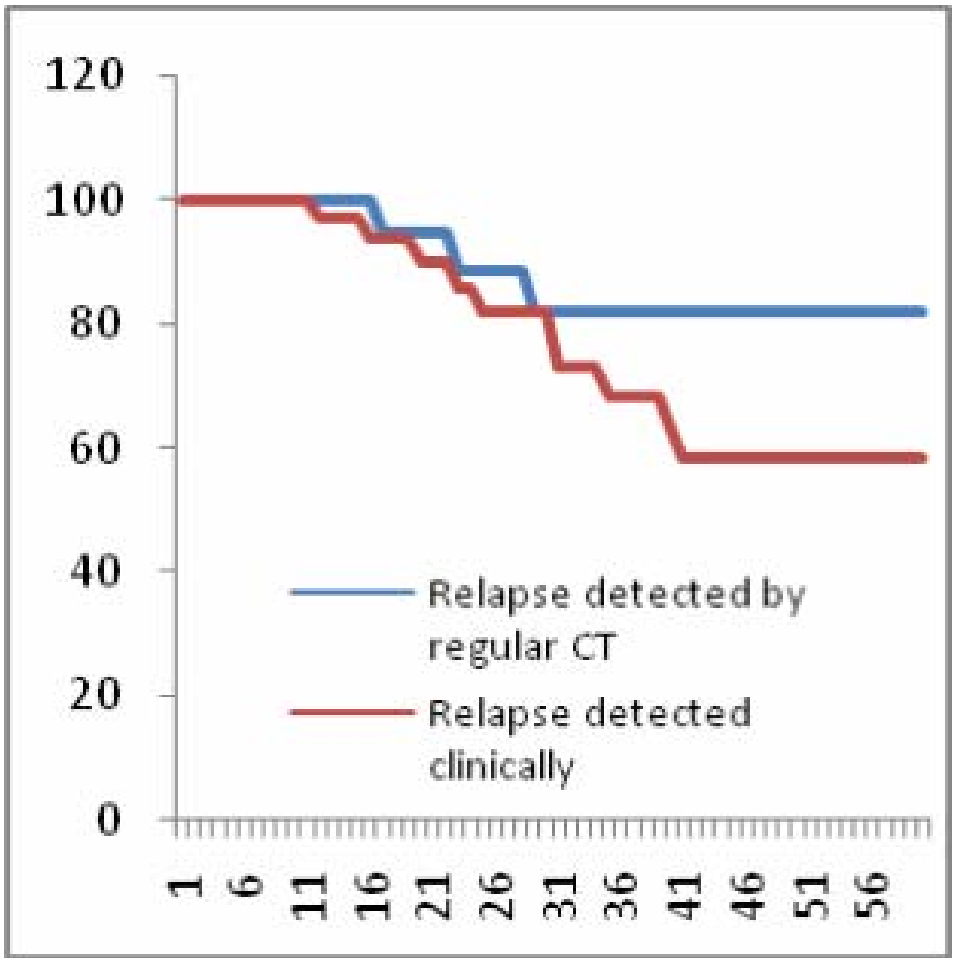

Figure. 5-year OS in the group of patients in which relapse was detected clinically or by regular CT

We performed the analysis of potential causes of this difference. Among them were: earlier relapse detection by routine CT, less advanced tumor spread, influence of the number of patients with early or late relapse, “adequacy” of relapse therapy and first-line therapy.

One of the reasons could be earlier relapse detection. For the purpose of analysis of this factor we studied time of relapse detection after the end of induction treatment, number of early relapses, and tumor dissemination (equivalence to the early (I-II) or advanced (III-IV) stages) in every group.

In the group in which relapse was suspected clinically time to relapse detection was 4-190 months, median 12 months, in the group in which relapse was detected by routine CT – 4-132 months, median 15 months ($p>0.05$). We performed the analysis of influence of early (relapse was suspected in the periodof4-12 months since end of the first-line therapy) or late (relapse was suspected after 12 months since end of the first-line therapy). There by relapses mostly were detected during first two years after the end of induction therapy.

The number of early relapses was comparable in both groups: 18 patients in the first group (50 %), and 10 patients in the second group (45 %), $p>0.05$.

More disseminated relapses were found in the first group (relapses detected clinically). Relapses with dissemination comparable to advanced stage of the disease were registered in this group in 22 of 36 patients (61 %), in the second group (relapses detected by routine CT) – in 11 of 22 patients (50 %), $p>0.05$.

During the evaluation of the “adequacy” of relapse treatment we allocated next arms: adequate treatment of relapse (second-line therapy with or without HDCT+AHSCT)

or inadequate treatment (patient refused therapy, palliative treatment or repeat of first-line therapy). During the evaluation of the "adequacy" of first-line treatment we used the criteria, which were described in our prior publication Kriachok I, Kushchevyi E. et al, 2011: absence of full staging, verification of lymphoma subtype with immunohistochemical analysis, inequality of treatment cycles to the lymphoma type or stage of the disease, absence of therapy changes in case of treatment failure, more then 8 cycles of first-line treatment, dose modification or drugs changes in the treatment cycles, breach of intervals between cycles, wrong radiation dose. [29]

During the analysis of therapy "adequacy" we found out that adequate relapse therapy was performed in 26 among 36 patients in the group of clinical relapse detection (72%) and in 14 among 22 patients (64%) in the group of regular CT relapse detection. The difference was insignificant.

The analysis of first-line therapy "quality" showed, that in the group of clinical relapse detection adequate treatment was performed in 18 among 36 patients (50%), and in 15 among 22 patients in the group of regular CT relapse detection (68%), $p>0.05$ (See Table 2).

Table 2. Principal factors, which have potential influence on patients' survival in the groups of patients in which relapse was detected clinically or by regular CT

Characteristic	Group of patients in which relapse was detected	Group of patients in which relapse was detected by	p>0.05

	clinically	regular CT	
Median time to relapse detection	12 months	15 months	
Number of early relapses	18 (50 %)	10 (45 %)	
Disease dissemination in the relapse: correspondence to the 3-4 stage	22 (61 %)	11 (50 %)	
«Adequacy» of the relapse treatment	26 (72 %)	14 (64 %)	
«Adequacy» of the first-line treatment	18 (5 %)	15 (68 %)	

Discussion and conclusions

Thereby, the most common type of relapse detection in all lymphoma subtypes is clinical suspicion (62 %). However, we found out significant difference in 5-year OS. 5-year OS was higher in the group where relapse was detected by routine CT (81.8±9.2%) in comparison with the group of clinically detected relapses (58.6±9.9%). We analyzed next potential causes of this difference: age, gender, presence of B-symptoms, histological type of lymphoma, stage of the disease at the moment of diagnosis, disease dissemination in the relapse, time of relapse detection,

“adequacy” of first-line and relapse treatment and so on. We didn’t find any significant difference between two groups. Nevertheless the tendency to the relapse detection on the earlier stages of the disease (50% vs. 39%) and major number of patients who received the “adequate” first-line treatment (68% vs. 50%) were observed in the group of CT relapse detection versus the group of clinical relapse detection. Probably exactly these reasons cause increased OS rate in the group in which relapse was detected by CT even despite of better treatment of relapse in the group of clinically detected relapses (64% vs. 72%).

According to published data the most effective schedule of patients’ observation after the end of lymphoma first-line treatment still isn’t defined. Majority of lymphoma recurrence are detected by clinical data. As distinct from published studies we received the results which showed that routine CT in the follow-up period allowed to reach the increase of OS. Possible causes of this peculiarity might be less diffused disease stage and bigger number of patients who received adequate first-line treatment in the group of patients in which regular CT was performed. Errors and low significance of our analysis data might be related to low number of patients in the studied group.

On our opinion the role of routine CT in the follow-up of lymphoma patients isn’t defined. Despite of high resolution and probability of relapse detection CT has significant shortcomings. Accept this according to the published data the majority of relapses still are detected clinically even with scrupulous CT screening. All these facts should be correctly weigh before final answer “To do or not to do” will be

given. More reliable results could be received in more scaled randomized studies which permit to evaluate distant results of patients' observation.

References:

1. Lister T.A., Crowther D., Sutcliffe S.B. et al. (1989) Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol., 7: 1630.
2. Garribba A.P. et al. (1990) Computerized tomography in the staging and the follow-up of Hodgkin's lymphoma of the thorax. Radiol Med. Dec., 80(6): 859-64.
3. Rezvani L. et al. (1986) Computed tomography in the diagnosis and follow-up of American Burkitt's lymphoma, 11(1): 36-40.)
4. Radford J.A., Eardley A., Woodman C. et al. (1997) Follow up policy after treatment for Hodgkin's disease: too many clinic visits and routine tests? A review of hospital records. BMJ, 314: 343-346.
5. Dryver E.T., Jernstrom H., Tompkins K. et al. (2003) Follow-up of patients with Hodgkin's disease following curative treatment: the routine CT scan is of little value. Br J Cancer, 89: 482-486.
6. Guadagnolo B.A., Punglia R.S., Kuntz K.M. et al. (2006) Cost-effectiveness analysis of computerized tomography in the routine follow-up of patients after primary ereatment for Hodgkin's disease. J Clin Oncol.,24: 4116-4122.

7. David C. Hodgson et al. (2010) A Population-Based Study of Follow-Up Care for Hodgkin Lymphoma Survivors Opportunities to Improve Surveillance for Relapse and Late Effects Cancer, 15: 3421.

8. Ng A., Constine L.S. (2010)ACR Appropriateness Criteria: follow-up of Hodgkin's lymphoma. Curr Probl Cancer, 34(3): 211-27.

9. Weeks J.C., Yeap B.Y., Canellos G.P., Shipp M.A. (1991) Value of follow-up procedures in patients with large-cell lymphoma who achieve a complete remission. J Clin. Oncol. 9: 1196–1203.

10. Nakamura K. et al. (2001) Relapse patterns of localized non-Hodgkin's lymphoma of the head and neck after clinical remission: results of a strict follow-up procedure. Int J Clin Oncol., 6(6): 302-305.

11. Elis A. et al. (2002) Detection of relapse in non-Hodgkin's lymphoma: role of routine follow-up studies. Am J Hematol., 69(1): 41-4.

12. Guppy A.E., Tebbutt N.C., Norman A., Cunningham D. (2003) The role of surveillance CT scans in patients with diffuse large B-cell non-Hodgkin's lymphoma. Leuk Lymphoma, 44: 123–125.

13. Armitage J.O., Loberiza F.R. (2006) Is there a place for routine imaging for patients in complete remission from aggressive lymphoma? Ann Oncol., 17(6): 883-884.

14. Choi J.Y. et al. (2011) The role of abdominal CT scan as follow-up after complete remission with successful Helicobacter pylori eradication in patients with H. pylori-positive stage I(E1) gastric MALT lymphoma. Helicobacter., 16(1): 36-41.

15. Goldschmidt N. et al. (2011) The role of routine imaging procedures in the detection of relapse of patients with Hodgkin lymphoma and aggressive non-Hodgkin lymphoma. Ann. Hematol., 90(2): 165-171.
16. Thompson C.A. et al. (2013) Utility of post-therapy surveillance scans in DLBCL. J Clin Oncol., 31: 8504.
17. Martin Hutchings (2011) Routine follow-up scanning of patients with lymphoma: who, when, how, and why? Leukemia & Lymphoma, 52(4): 552–553.
18. Beyan C. et al. (2007) The effect of radiologic imaging studies on the risk of secondary malignancy development in patients with Hodgkin lymphoma, 7(7): 467-469.
19. Clinical Practice Guidelines for the Diagnosis and Management of Lymphoma The Cancer Council Australia/Australian Cancer Network 2005 http://www.nhmrc.gov.au/guidelines/publications/cp107
20. Torrey M.J., Poen J.C., Hoppe R.T. (1997) Detection of relapse in early-stage Hodgkin's disease: role of routine follow-up studies. J Clin Oncol., 15: 1123-1130.
21. Eichenauer D.A., Engert A., Dreyling M. (2011) Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, 22 (6): vi55–vi58.
22. NCCN Clinical practice guidelines in oncology Hodgkin's Lymphoma. Version I.2013.

23. Ghielmini M., Vitolo U., Kimby E. et al. (2013) ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). Ann. Oncol., 24: 561–576.
24. Dreyling M., Thieblemont C., Gallamini A. et al. (2013) ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. Ann. Oncol., 1–21.
25. Dreyling M., Ghielmini M., Marcus R., Salles G., Vitolo U. (2011) Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol., 22 (6): vi59–vi63.
26. Zucca E., Dreyling M. (2010) Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol., 21 (5): v175–v176.
27. Willemze R., Dreyling M. (2010) Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol., 21(5): v177–v180.
28. Tilly H., Vitolo U., Walewski J., Gomes da Silva M., Shpilberg O., André M., Pfreundschuh M., Dreyling M. (2012) Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol., 23 (7): vii78–vii82.

29. NCCN Clinical practice guidelines in oncology Non-Hodgkin's Lymphoma. Version I.2013.
30. Крячок И.А., Кущевой Е.В. и соавт. (2011) Опыт применения схем терапии II линии при лечении рецидивов и рефрактерного течения лимфом. Клиническая онкология, 2(2): 62-66.