The Egyptian Journal of Hospital Medicine (October 2017) Vol.69(1), Page 1668-1673

Role of Surveillance CT in Detection of Pre-Clinical Relapse in Patients with B-Cell lymphoma: A Retrospective Study

Ahmad Hassan Soliman ,Shorouq Sabry Rizq Aly
Department of Radiodiagnosis, Faculty of Medicine
Ain Shams University
Corresponding author: Dr.Ahmad Hassan Soliman, MD, Telephone No.:01110009147 e-mail: DrSoliman@hotmail.com

ABSTRACT

Background: with the evolution of curative treatment regimen, the rate of complete remission achieved in patients with diffuse aggressive non-Hodgkin lymphoma is continuously rising. It is achievable at the end of primary treatment in about 60-80%. On the other hand relapse is very common in the 1st two years after end of primary treatment in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, that is to say, about 20-25% of patients relapse after complete response. Use of routine surveillance imaging for relapse detection is still an area of controversy. Evidence is still lacking to support the utility of routine imaging (namely CT scan) in detection of pre-clinical relapse in diffuse aggressive non-Hodgkin lymphoma (NHL). This work aims at adding further evidence to the pool of studies available in the literature which might encourage, or disapprove the rule of CT as a routine imaging procedures in lymphoma patients who achieved CR.

Objectives: I. To clarify whether surveillance CT scan has a significant role in early detection of asymptomatic relapse in B-Cell lymphoma patients. II. To assess the contribution of image-based relapse detection to the overall survival of B-Cell lymphoma patients**.**

Design: this is a retrospective cohort study in which 50 Patients with B-Cell lymphoma diagnosed between 2014 and 2016 were selected from the PACS of Radiology Department at Ain Shams University Hospitals. Age ranges between 20 and 70 year-old. All diagnoses were confirmed by histopathology studies. All patients underwent treatment and follow-up strategy as planned by their treating oncologist/hematologist, after which they entered CR or SD according to IWG Cheson criteria of treatment response. Disease progression was retrospectively reviewed over a period of 6 months up to 2 years. Surveillance CT scan was performed on the neck, chest, abdomen and pelvis on each of the planned follow-up visits. Relapses were defined as "asymptomatic" if there were no reported symptoms and a normal examination was recorded.

Results: the most common cause of relapse detection was patient-reported symptoms alone (41%) or in combination with abnormal blood tests and/or physical examination (23%). Routine imaging was responsible for relapse detection in 27% of the patients. The unadjusted median OS for patients with imaging-detected relapse was 90 months versus 38 months for patients non imaging-detected relapse (P = 0.0008). Although surveillance imaging proved no significance in detection of pre-clinical relapse, our regression analysis showed that it remained significantly associated with reduced risk of death.

Conclusion: clinical symptoms remain the leading factor in diagnosing recurrent lymphoma in the era of modern imaging, and this study questions the clinical relevance of current practice. A possible survival advantage was seen for patients with image-detected relapse.

Keywords: Non-Hodgkin lymphoma, Relapse, CT scan.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a fairly common tumor that accounts for 4.3% of all new cancer cases per year in USA. Its incidence is almost doubling annually [(1)]. In Egypt, lymphoma is the fourth most common tumor in adults, with B-Cell lymphoma being the commonest subtype of NHL accounting for about 49% of all NHL cases presenting to NCI [(2)].

With such a disease burden, and about one third relapsed NHL patients after complete remission, on-going research on new methods of detection, staging and response assessment is always making the highlights, with relapse detection being of major concern, especially with the new curative methods made available for relapsed cases. The high risk of radiation induced malignancies associated with frequent radiological follow-up scans for those long term survivors also raised the red flag for re-establishing a risk-benefit oriented follow-up plan for those patients [(3)].

Careful history taking, thorough physical examination and good clinical judgment are the cornerstones of an appropriate follow-up. Many

Received:8 / 4 /2017
Accepted:17 / 4 /2017
DOI : 10.12816/0040117

recommendations have been published for formulating follow-up plans according to histology; curable versus non-curable. For curable conditions (HL, DLBCL) the likelihood of relapse decreases with time, so the frequency of follow-up decreases accordingly, and the contrary goes for non-curable conditions (mantle cell lymphoma and follicular lymphoma) [(4)].

Although most guidelines do not recommend whole body CT scan as part of routine follow-up for patients who went through complete remission, it is still adopted by many clinicians as part of their patients' follow-up visits. However, its value for assessment of early asymptomatic relapse is questionable, let alone its influence on the overall outcome compared to other modalities of relapse detection [(5)].

Generally speaking, CT scan is routinely used in follow up of NHL for early detection of radiological relapse. Nevertheless, till the most recent publication in the literature, there is not a single well-established standard follow up protocol for early detection of relapse. Despite the large number of studies discussing the value of CT, FDG-PET and PET/CT in follow up of NHL, use of routine surveillance imaging for relapse detection is still an area of controversy [(4)].

Early detection of relapse is very important because patients who achieve CR have an overall survival similar to normal population, with the only exception of having higher risk of relapse (about 30%) in the first two years following primary treatment [(3)].

In the most recent systematic review analysis comparing studies which evaluated the role of surveillance CT scan in detection of relapse, the greatest number of relapses were detected following patient-reported symptoms outside regular follow up visits (about 60% of all relapsed cases), while CT could detect relapse before clinical manifestations in a small portion of cases (30%) [(5)].

Furthermore, there was no statistically significant difference in overall survival (OS) between symptom-based relapse and imaging-based relapse, which brought the routine use of CT scan in surveillance of patients after completion of first-line therapy into questioning [(6)].

This uncertainty regarding use of routine imaging in surveillance of diffuse aggressive NHL after achieving CR at the end of first line therapy was further enriched by estimated long-term risk of developing secondary malignancy due to excessive exposure to radiation. This was evaluated in 2007 by Brenner and Hall [(15)] who estimated that 2% of all cancers can be attributable to radiation from CT scans in an analysis relying on organ-specific cancer incidence and mortality in atomic bomb survivors.

In addition the risk of secondary malignancy due to repetitive radiation exposure, there is increased risk of complicated biopsies taken in in-determined image-based relapse, with the estimated increased number of lymphoma survivors who will be added to the pool of surveillance which imposes more pressure on the health community for identifying an appropriate surveillance plan [(2)].

Patients of lymphoma are divided into two groups according to the subtype of the disease and the received treatment; those who receive curative-intent treatment having aggressive NHL and HL, and those who do not receive curative intent treatment as they have an indolent NHL and mantle cell lymphoma as well as those who cannot tolerate aggressive induction therapy [(3)].

Diffuse large B-cell Lymphoma (DLBCL) is the most common aggressive NHL subtype, with its outcomes varying according to the International Prognostic Index at time of staging. There is a study which stated that stage III/IV disease, lactate dehydrogenase (LDH) level above the upper limit of normal, age >60 years, ECOG performance status ≥2 and involvement of >1 extranodal site as poor prognostic factors for DLBCL [(7)].

The rational of a successful surveillance is based on the assumption that firstly, it should detect relapse prior to manifestation of clinical symptoms, and secondly it should be linked to proper available treatment options in early stages to provide better outcomes as regards the overall survival and decrease risk of death in relapsed patients detected prior to development of clinical symptoms [(8)].

Unfortunately, applying this rational on patients with aggressive NHL is somehow challenging, as the biological nature of the disease tends to have a more aggressive clinical presentation before imaging features are indicative of a positive relapse. Besides, it is still a matter of controversy whether early detection of relapse is associated with better overall survival (OS) outcome [(8)].

Considering the aggressive nature of DLBCL, relapse is almost often detected based on patient reported symptoms, and it is very unlikely

for routine imaging follow-up to detect relapse in absence of clinical manifestation [6].

Therefore, The recently reported Lugano classification advice against the use of routine surveillance scans in the absence of a clinical indication, and this recommendation was considered in the most recent version of the National Comprehensive Cancer Network (NCCN) guidelines for management of patients with early-stage DLBCL while the guidelines continue to allow CT's every 6 months for the first 2 years after treatment for patients in complete remission (CR) [4].

Although role of routine imaging is well-established in pre-treatment assessment of lymphoma patients, the value of CT and FDG-PET in follow up is not well-established yet. However, contrast enhanced thoraco-pelvi-abdominal CT scan is the most common routinely used imaging modality in follow up of DLBCL for relapse in patients with complete remission [7].

AIM OF THE STUDY

I. To clarify whether surveillance CT scan has a significant role in early detection of asymptomatic relapse in B-Cell lymphoma patients.

II. To assess the contribution of image-based relapse detection to the overall survival of B-Cell lymphoma patients.

PATIENTS AND METHOD

The present study was approved by the Ethics Board of Ain Shams University.

It is a retrospective study that included 50 patients from PACS of Radiology department at Ain Shams University Hospital. The inclusion criteria were as follows: (a) primary diagnosis of large B-cell lymphoma between 2014 and 2016; (b) age above 15 years at diagnosis; (c) complete remission (CR) or CR unconfirmed (CRu) on first-line therapy; and (d) lymphoma relapse during the follow-up period.

Follow-up protocol and imaging: Regular follow-up evaluations were conducted after completion of therapy. As a rule, patients were seen quarterly for the first 2 years of follow-up and biannually from the third to the fifth year. The follow-up evaluations included symptom assessment, physical examination, and blood tests. Concomitant surveillance imaging procedures were mainly performed with computed tomography (CT) every 3 months for the first 2 years of follow-up during the inclusion period then every 6 months till the 5th year of follow up. Final decisions regarding follow-up practice were as described by the treating physicians.

Outcome

Relapse detection was attributed to patient-reported symptoms when relapse investigations were initiated as a result of symptoms or findings reported by the patient. Relapse detection could also be attributed to patient-reported symptoms in combination with abnormal physical examination and/or blood tests. When routine imaging was first to suggest recurrent lymphoma, the relapse was registered as being imaging detected. A routine imaging study was defined as a neck-chest-pelvi-abdomen CT study prescribed to patient in clinical remission. Other causes of relapse detection were isolated abnormal routine blood tests or physical examination. In the statistical analyses, the term "imaging-detected relapse" refers to patients with imaging-detected relapse, whereas "non-imaging-detected relapse" refers to all others. Unscheduled visits were defined as visits requested by patients or relatives outside preplanned follow-up visits and acute hospital admissions.

Statistical analysis

Differences between groups of categorical and continuous variables were tested with Chi-Square test and t-test, respectively. Overall survival (OS) was defined as the time from first lymphoma diagnosis (not from time of relapse) until death of any cause. Regression analyses were performed to examine the prognostic significance of relapse detection method. Statistical analyses were performed with Stata version 12.

RESULTS

Patients' Characteristics:

A total of 50 patients were eligible for inclusion in this study. Relapse was biopsy-verified in 86% of the patients, whereas relapse diagnosis relied on clinical symptoms and/or imaging in 14% of the patients. The baseline characteristics (characteristics at the time of first lymphoma diagnosis) of the 50 included patients are shown in Table 2.

Table 1: Baseline patient's characteristics

Baseline characteristics	All (n=50)
Median age in years (range)	62 (20-90)
Gender (percentage)	
Male	48%(24)
Female	52%(26)
Treatment	
Chemotherapy only	40
Radiotherapy only	2
Combined chemo-radiotherapy	8
Remission Status after 1st line therapy	
CR	36
Cru	14

Table 2: relapse characteristics and relapse detection method

Relapse characteristics	All patients (n=50)
Median time to relapse (months)	8
Time of relapse in percentage (%)	
1st year after follow up	60
2nd year after follow up	21
After 2nd year of follow up	19
Median no. of routine imaging procedure (range)	1 (0-15)
Relapse detection method in (%)	
Routine imaging	27
Others	73

Relapse Detection methods and relapse characteristics:

A detailed overview of time to relapse, relapse detection methods, and relapse characteristics are given in Table 18. The median time from response assessment till relapse was 8 months for all patients. The majority of patients relapsed within the first year of follow-up (60%); however, lymphoma recurrences were still diagnosed after the second year of follow-up (19%). Relapse after the fifth year of follow-up only occurred in four patients with DLBCL.

The most common cause of relapse detection was patient-reported symptoms alone (41%) or in combination with abnormal blood tests and/or physical examination (23%). Routine imaging was responsible for relapse detection in 27% of the patients with no significant differences between the diagnostic subgroups. Detection of relapse was rarely attributed to abnormal blood tests or physical examination alone. The relapse investigations were initiated on preplanned visits in 48% of all patients (Table 3). Among patients with imaging-detected relapse, (10%) had developed symptoms by the time receiving the imaging results. The absence of symptoms at the time of first lymphoma diagnosis was not associated with a later imaging- detected relapse (P 0.78).

Outcome according to relapse detection method:

The unadjusted median OS for patients with imaging-detected relapse was 90 months versus 38 months for patients nonimaging-detected relapse (P = 0.0008). Although surveillance imaging proved no significance in detection of pre-clinical relapse, our regression analysis showed that it remained significantly associated with reduced risk of death.

DISCUSSION

Aims of this study were to investigate the role of post-therapy surveillance imaging in patients with large B-Cell lymphoma. In a review of relapse patients, we confirm that patient-reported symptoms still prompt the suspicion of disease recurrence in the majority of patients and that the indiscriminate use of surveillance imaging is associated with high costs with no significant value in detection of pre-clinical relapse [(9)].

With the evolution of curative treatment regimen, the rate of complete remission achieved in patients with diffuse aggressive non-Hodgkin lymphoma is continuously rising. It is achievable at the end of primary treatment in about 60-80% [(6)].

On the other hand relapse is very common in the 1st two years after end of primary treatment in DLBCL and follicular lymphoma, that is to say, about 20-25% of patients relapse after complete response [7]. Luckily enough, relapsed cases are still

eligible for curative treatment using a salvage regimen of second-line chemotherapy and/or radiotherapy followed by stem cell autologous BM transplantation [8].

All these facts made early follow up after end of treatment and assessment of response a very crucial step in early detection of relapse while it is still of lower health and economic burden which in turn saves patients' money and improves his chances in receiving curative management [9].

Routine follow up plan usually implies history and clinical examination every 3 months for 1 year, and every 6 months for 2 more years and then once a year. This is done alongside complete blood count carried out at 3, 6, 12 and 24 months, then only as needed if clinically suspicious symptoms arise in patients who are eligible for further treatment. Minimal radiological follow up at 6, 12, 24 months by CT after complete response is the routine practice although evidence is lacking whether it helps in early detection of relapse, and whether early radiological relapse detection improves the overall survival of diffuse NHL patients [10].

An unexpected possible survival advantage was noted among patients whose relapse detection was based on CT surveillance scans. Early studies reported that routine radiological studies detected only 3–30% of lymphoma relapses and concluded that rational surveillance strategies should be based on careful listening for symptoms and physical examination, and that the use of CT surveillance accounts for diagnosis of only 9–26% of relapsed NHL. These numbers are consistent with the results of the current study where surveillance imaging was important to the detection of 27% of relapse.

Significant healthcare resources are spent on post-therapy lymphoma surveillance [11]. As expected, the price per imaging-detected relapse was higher in the second year of follow-up as most patients relapse during the first year.

When looking at all patients in CR/CRu entering follow-up in the current study, the proportion of patients who later experienced an imaging-detected relapse was very small. Limiting the use of surveillance imaging to patient groups with high a priori risk of relapse and only for patients eligible for effective salvage therapies may increase the cost effectiveness. In addition, routine imaging should not be used beyond the first 2 years of follow-up as few patients relapse after this period.

The costs and potential harm associated with surveillance imaging can be justified if early relapse detection improves outcome [12]. Therefore, it is rational to believe that early relapse detection will improve outcome by virtue of reduced tumor burden and better performance status. We found a trend toward better outcome in patients with NHL with imaging-detected relapse; however, the low number of patients does not allow any firm conclusions to be drawn. In the current study, we were therefore surprised to see a 40% risk reduction for death among patients with DLBCL with imaging-detected relapse.

The low median number of routine imaging studies performed in the current study population of relapse patients does not reflect a restrictive use of surveillance imaging or non-adherence to local protocols, but rather the fact that relapse mainly occurs early in the follow-up period and sometimes before the first surveillance imaging [13].

The available evidence from literature is all obtained from retrospective studies and very few prospective studies. This evidence couldn't recommend CT scan as a solid procedure in follow up for relapse detection, as in most studies relapse detection was mainly based on clinical manifestations, and CT scan could detect pre-clinical relapse in only few patients [14].

On the other hand, another study [15] proved that although relapse was detected by CT alone in only a minority of patients (22.2%), these patients were 4.1 times more likely to have a low risk disease (by sAAIPI) and a more chemosensitive disease compared to the group in which relapse was detected by either clinical symptoms or laboratory abnormality.

Another study [16] stated that patients in which relapse was detected by CT prior to development of clinical symptoms had lower risk of death than those in which relapse was based on non-imaging modalities.

The most important limitations of this study are the weaknesses due to its retrospective design and small number of the population studied. By defining imaging-detected relapse as a relapse where routine imaging was first to raise suspicion of disease recurrence, we avoided the bias in symptom registration likely to occur in awareness of imaging results.

CONCLUSION

In conclusion, clinical symptoms remain the leading factor in diagnosing recurrent lymphoma in the era of modern imaging, and this study questions the cost effectiveness of current practice. However, restricting the use of surveillance imaging to patients at high risk of relapse and eligible for effective salvage therapies could tip the balance toward a better risk/benefit ratio. Interestingly, a possible survival advantage was seen for patients with imaging-detected relapse, although firm conclusions about the causal role of imaging cannot be drawn from a retrospective study. Therefore, this study certainly does not encourage the use of more surveillance imaging in general but strongly emphasizes the need for prospective randomized trials to clearly define the role of surveillance imaging in lymphoma.

REFERENCES

1. **Armitage JO (2005):** Staging non-Hodgkin lymphoma. CA: A Cancer Journal for Clinicians, 55(6) :368–76. https://doi.org/55/6/368 [pii]
2. **Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Müeller SP, Cheson BD (2014):** Role of imaging in the staging and response assessment of lymphoma: Consensus of the international conference on malignant lymphomas imaging working group. Journal of Clinical Oncology, 32(27): 3048–3058. https://doi.org/10.1200/JCO.2013.53.5229
3. **Bonadonna G (2000):** Historical Review of Hodgkin's Disease. British Journal of Haematology, 110(3) :504–511. https://doi.org/10.1046/j.1365-2141.2000.02197.x
4. **Brenner DJ & Hall EJ (2007):** Current concepts - Computed tomography - An increasing source of radiation exposure. New England Journal of Medicine, 357(22): 2277–2284. https://doi.org/10.1056/NEJMra072149
5. **Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H & Jaffe ES (2011):** The 2008 WHO classification of lymphoid neoplasms and beyond: Evolving concepts and practical applications. Blood, 117(19) :5019–5032. https://doi.org/10.1182/blood-2011-01-293050
6. **Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E & Lister TA (2014):** Recommendations for initial evaluation, staging, and response assessment of hodgkin and non-hodgkin lymphoma: The lugano classification. Journal of Clinical Oncology, 32(27): 3059–3067. https://doi.org/10.1200/JCO.2013.54.8800
7. **Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, Canellos GP (1999):** Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. Journal of Clinical Oncology, 17(4): 1244–1253. https://doi.org/10.1200/JCO.1999.17.4.1244
8. **Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Diehl V (2007):** Revised response criteria for malignant lymphoma. Journal of Clinical Oncology, 25(5): 579–586. https://doi.org/10.1200/JCO.2006.09.2403
9. **Cohen JB, Behera M, Thompson CA & Flowers CR (2016):** Evaluating surveillance imaging for diffuse large B-cell lymphoma and Hodgkin lymphoma. Blood, 129(5) :561–565. https://doi.org/10.1182/blood-2016-08-685073
10. **Cohen JB & Flowers CR (2014):** Optimal disease surveillance strategies in non-Hodgkin lymphoma. Hematology, 214(1) :481–487. https://doi.org/10.1182/asheducation-2014.1.481
11. **Cohen JB, Kurtz DM, Staton AD & Flowers CR (2015):** Next-generation surveillance strategies for patients with lymphoma. Future Oncology, 11(13): 1977–1991. https://doi.org/10.2217/fon.15.92
12. **Crowther D & Lister TA (1990):** The Cotswolds report on the investigation and staging of Hodgkin's disease. British Journal of Cancer, 62(4): 551–2. https://doi.org/10.1038/bjc.1990.328
13. **Dong A, Xiao Z, Yang J, & Zuo C (2016):** CT, MRI, and 18F-FDG PET/CT Findings in Untreated Pulmonary and Hepatic B-Cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT) Over a Five-Year Period: A Case Report. Medicine (Baltimore), 95(12):e3197. https://doi.org/10.1097/md.0000000000003197
14. **Dupas B, Augeul-Meunier K, Frampas E, Bodet-Milin C, Gastinne T, & Le Gouill S (2013):** Staging and monitoring in the treatment of lymphomas. Diagnostic and Interventional Imaging, 94(2): 145–157. https://doi.org/10.1016/j.diii.2012.12.009
15. **Thompson CA, Ghesquieres H, Maurer MJ, Cerhan JR, Biron P, Ansell SM, Link BK (2014):** Utility of routine post-therapy surveillance imaging in diffuse large B-cell lymphoma. Journal of Clinical Oncology, 32(31): 3506–3512. https://doi.org/10.1200/JCO.2014.55.7561
16. **Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, Ladetto M (2015):** Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO, 26(5): v116–v125. https://doi.org/10.1093/annonc/mdv304.