Standardized CT evaluation of lymphnodes in untreated chronic lymphocytic leukemia (CLL)

Poster No.: C-1708
Congress: ECR 2011
Type: Scientific Paper
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Keywords: Haematologic, Lymph nodes, CT, Structured reporting, Staging, Haematologic diseases, Leukaemia
DOI: 10.1594/ecr2011/C-1708

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Purpose

Since the 80s, chronic lymphocytic leukemia (CLL) staging and treatment decision have been relying on clinical and biological findings, i.e. presence of superficial lymph nodes, hepatosplenomegaly and/or cytopenias. Nonetheless, computed tomography (CT) has been widely used for evaluation of response and relapse after treatment, and published data on its interest have been contradictory\textsuperscript{1,2}. In fact, conversely to what was done for Non Hodgkin Lymphomas, CT findings at initial staging in CLL untreated patients have never been clearly described.

The purpose of this study is to define a standardized quantification system based on size and location of lymph nodes (LN) in order to identify patients at risk of progression in CLL.
Methods and Materials

Patients

Helical CT of the thorax, abdomen and pelvis were performed in a prospective study of 66 previously untreated CLL followed in the same institution for which complete clinical, biological and prognostic annotations were available.

CT evaluation

1) CT technique and interpretation: CT examinations were performed in different radiologic institutions using various helical CT scanners and acquisition protocols. The studies were routinely acquired 70 seconds to 90 seconds after the injection of 100 to 150 ml of iodinated contrast material concentrated at 300 to 350 mg/ml and at a rate of 2 to 3 ml/second by powered injection.

Axial slices with a thickness of 5 mm or less were mainly used for interpretation on a PACS workstation by scrolling through the images, as well as coronal and sagittal reconstructions when available. Three radiologists independently evaluated the CT scans, not having any information of the clinical status or disease evolution. In the rare cases in which there was some discrepancy in their evaluation of the CT scan images, a consensus description was achieved.

2) Nodal localisation

Nodal areas were defined according to the "Follicular Lymphoma International Prognostic Index" (FLIPI) definitions of nodal sites for axillary, mediastinal, mesenteric, inguinal locations. Instead "paraaortic" FLIPI nodal site was split into paraaortic, and iliac groups.

The anatomic location of the largest LN in each FLIPI nodal site was specified. In fact FLIPI nodal site includes different anatomic sites. So "mesenteric" FLIPI nodal site includes anatomic mesenteric location and others intraabdominal LN, "mediastinal" FLIPI nodal site includes mediastinal, hilar and retrocrural LN, "inguinal" FLIPI nodal site includes inguinal and femoral LN.

3) Nodal size

Following international standard criteria, lymph nodes were considered abnormal when their maximum short axis dimension measured one centimeter or more. The two
maximum orthogonal axes of the largest abnormal LN were measured and their product calculated in each nodal site.

Furthermore in each nodal site, a grading scale inspired by the classical malignant retroperitoneal lymphadenopathy depiction estimated amount of LN$^{10}$:

- **Grade 1**: one or several discrete enlarged lymph nodes,
- **Grade 2**: a more conglomerate group of contiguous enlarged nodes,
- **Grade 3**: a large homogeneous mass in which individual nodes are non longer recognizable.

4) **Aspect of LN** (such as necrosis and calcifications) and mass effect on surrounding structures were also analysed.

5) **Splenomegaly** was assessed by the height of the spleen superior to 12 centimeters$^{11}$ associated with a rounded appearance. Splenic nodules were also noted. **Hepatomegaly** was evaluated by visual assessment associated with liver height exceeding 15 centimeters in its craniocaudal extent. Splenomegaly and hepatomegaly were not taken in account for CLL CT status evaluation when they could be readily explained by other etiologies such as portal hypertension and cirrhosis.
Results

1) Grading scale is illustrated on figures 1 to 8.

- **Figure 1 on page 7**: axillary LN grade 1 versus grade 2.
- **Figure 2 on page 7**: mediastinal FLIPI nodal area grade 1 versus grade 2.
- **Figure 3 on page 8**: mesenteric FLIPI nodal area (porta hepatis nodes) grade 1 versus grade 2.
- **Figure 4 on page 9**: mesenteric FLIPI nodal area (mesenteric nodes) grade 1 versus grade 2 shown on axial slices.
- **Figure 5 on page 10**: mesenteric FLIPI nodal area (mesenteric nodes) grade 1 versus grade 2 shown on coronal slices (respectively same patients as in fig. 4).
- **Figure 6 on page 11**: paraaortic LN grade 2 versus grade 3 shown on axial slices.
- **Figure 7 on page 12**: paraaortic LN grade 2 versus grade 3 shown on coronal slices (respectively same patients as in fig. 6).
- **Figure 8 on page 13**: inguinal LN grade 1 versus 2.

2) Localisation and size of LN:

Frequency, size and grade of LN in bilateral areas (axillary, iliac, inguinal) were similar for both sides.

**a) Superficial LN** were more frequently involved in axillary than inguinal areas (75% versus 50%).

**b) Mediastinal LN** (53%) appeared less frequent than other deep LN: iliac 68%, mesenteric 64%).

Furthermore, these nodes were rarely prominent. In 75 % cases, mean maximum short axis was inferior to 15 millimeters.

In 2/66 cases only, mediastinal LN were considered as grade 2, and in 1/66 only as bulky, according to the current definition in CLL of at least 5 cm in size. In this case, they were located in the subcarinal area. No significant LN was found in mediastinal anterior anatomic site as usual seen in Non Hodgkin lymphoma thoracic involvement.

**c) Abdominal LN**: Interestingly, mesenteric area was more frequently involved than paraaortic LN (64 % versus 55%) and their size was significantly larger: Mean longest
axis and product of the two maximum orthogonal axes of the largest abnormal LN were significantly higher in mesenteric than in paraaortic site (respectively 31 mm versus 18.5 mm and 589 mm$^2$ versus 228 mm$^2$).

When considering the site of the largest node for each patient, mesenteric area was by far the most frequent (27%) (Cf. table in figure 9 on page 14)

3) Correlation between CT patterns and IGVH gene mutational status

IGHV gene mutational status accounts for the gold standard prognostic factor in CLL. Unmutated IGVH status is strongly linked with adverse evolution.

Presence of deep LN was strongly related to IGVH gene mutational status (p=0.0001). LN were more frequently noted in patients with unmutated than mutated IGHV genes. It was particularly the case in the paraaortic area (80% versus 22%, p=0.00009).

When present though, LN had similar median size whether patients had mutated or unmutated IGVH genes. But interestingly their pattern differed as grade 2 or 3 was exclusively observed in unmutated cases.

4) CT findings and evolution

Mean follow-up of the 66 patients was 50 months. Half of them progressed and required therapy.

Presence of superficial grade 1 was not discriminant as they were present in all patients with progressive disease and 60% of stable CLL.

Conversely, presence of deep LN was significantly associated with progressive disease i.e. mesenteric (88% vs 42%, p=0.0005), paraaortic (79% vs 33%, p=0.0002), mediastinal (70% vs 33%, p=0.004).

Splenomegaly (25/66 cases), was always associated with mesenteric lymph nodes except in one patient.

35/50 patients with deep LN already required therapy while none of the 17 others experienced progression to date.
Images for this section:

**Fig. 0:** Axillary LN. (a) grade 1. (b) grade 2.

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**Fig. 0:** Mediastinal FLIPI nodal area. (a) grade 1. (b) grade 2.

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Fig. 0: Mesenteric FLIPI nodal area (porta hepatis nodes). (a) grade 1. (b) grade 2.

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**Fig. 0:** Mesenteric FLIPI nodal area (mesenteric nodes). (a) grade 1. (b) grade 2. Same patients are respectively illustrated by coronal slices on figure 5a and 5b.

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**Fig. 0:** Mesenteric FLIPI nodal area (mesenteric nodes). (a) grade 1. (b) grade 2. Same patients are respectively illustrated by axial slices on figure 4a and 4b.

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**Fig. 0:** Paraaortic LN. (a) grade 2. (b) grade 3. Note infiltrative retroperitoneal mass associated with grade 2 mesenteric nodes (dotted arrow). Same patients are respectively illustrated by coronal slices on figure 7a and 7b.

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Fig. 0: Paraortic LN. (a) grade 2. (b) grade 3. Same patients are respectively illustrated by axial slices on figure 6a and 6b.

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**Fig. 0:** Inguinal LN. (a) grade 1. (b) grade 2.

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Fig. 0: Site of the largest lymphnode for each patient

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Conclusion

Some lymph node CT patterns of CLL appear different from those encountered in other Non Hodgkin lymphomas\textsuperscript{13}. CLL lymph node involvement is not prominent in thorax, especially in mediastinal anterior site.

In our previously untreated patients few bulky masses were observed\textsuperscript{14}. Mesenteric LN involvement was more frequent and their size larger than paraaortic LN, comforting the notion of a predominant role of antigen exposition in CLL pathophysiology. But presence of paraaortic LN was of adverse significance and association with rapid progression. Moreover grading pattern was of prognostic interest: LN had similar median size when present whether patients had mutated or unmutated IGVH genes but grade 2 or 3 pattern was exclusively observed in unmutated cases and strongly associated with adverse prognosis.

In conclusion, this description and grading system has a strong prognostic significance and will be of great help in assessing initial staging and further post therapeutic evaluation.
References


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