Imaging techniques to characterize spleen involvement in patients with Hodgkin lymphoma

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Spleen invasion in Hodgkin lymphoma

Issue 1: How is splenomegaly defined?

Issue 2: What is the best imaging technique to detect splenic focal lesions?

Issue 3: What is the best imaging tool to characterize the nodules in the spleen?
Issue 1: How is splenomegaly defined?

Availability of different tools for sizing the spleen!

Palpation: ≥1 cm from the costal border (in the midclavicular line), but it is associated with 35%-40% false-negative findings*

*Picardi M et al. Haematologica 2003; 88: 794-800
Ultrasonography scan: excellent tool for sizing the spleen

• Easy to perform in routine practice (at the patient’s bedside)
• Safe: no ionizing radiation
• Less expensive than radiological tools
• Performable by hematologists

Picardi M et al. Bone Marrow Transplantation 1999; 24: 173-177
Picardi M et al. Blood 2002; 99: 4228-4230
Picardi M et al. Haematologica 2003; 88: 794-800
Issue 1: How is splenomegaly defined?
Ultrasonography-calculated splenic volume
Ultrasonography-measured longitudinal diameter

Results in 30% of false-negative findings*

Spleen may have various shapes*

*Picardi M et al. Blood 2002; 99: 4228-4230
*Picardi M et al. Haematologica 2003; 88: 794-800
Spleen sizing by ultrasound scan and risk of pneumococcal infection in patients with chronic GVHD: preliminary observations

M Picardi, C Selleri and B Rotoli

Division of Hematology, Federico II University Medical School, Naples, Italy

Measurement of spleen volume by ultrasound scanning in patients with thrombocytosis: a prospective study

Marco Picardi, Vincenzo Martinelli, Rosanna Ciancia, Ernesto Soschia, Roberto Morante, Antonio Sodano, Giuliana Fortunato and Bruno Rotoli

Spleen enlargement following recombinant human granulocyte colony-stimulating factor administration for peripheral blood stem cell mobilization

Marco Picardi, Gennaro De Rosa, Carmine Selleri, Nicola Scarpato, Ernesto Soschia, Vincenzo Martinelli, Rosanna Ciancia, Bruno Rotoli

Haematologica 2003; 88: 794-800
US-calculated splenic volume (mL)

50 healthy volunteers

Median, 173 mL (range, 50–400)
VAR1 vs. VAR2 (Casewise MD deletion)

VAR2 = 28,745 + 0.87897 * VAR1

Correlation: $r = 0.98499$

US-calculated splenic volume inter-observer variability
R = 0.9
P < 0.0001
Issue 1: How is splenomegaly defined?

Ultrasonography-calculated volume: >400 mL

Splenomegaly may occur even if the spleen is not affected by HL (hyperplastic or congestive enlargement), and involvement does not necessarily imply spleen enlargement*

Issue 2: What is the best imaging technique to detect splenic focal lesions?

Excellence in ultrasound imaging techniques:
• High resolution
• Real-time tissue harmonic compound
• SonoCT
• Contrast-enhanced
The ultrasonography features of splenic focal lesions

One or more distinct hypoechoic, ovoid, well-circumscribed, macro-nodule (>1 cm) or micro-nodule (≤1 cm) by measuring the long axis.

Nodule behaves differently at i.v. infusion of contrast agent containing sulfur hexafluoride-filled phospholipid-stabilized microbubbles, including the arterial phase (starting 10 sec after injection) and the parenchymal phase (starting 40 sec after injection, until 7-9 min)

Picardi M et al. Radiology 2009; 251: 574-582
Nonenhanced harmonic compound US shows 1 cm nodule

Staging in a patient with HL: focus on spleen (FDG PET

Color-Doppler examination
Perfusion (arterial and parenchymal) phase contrast-enhanced US shows the isoechoic and isoenhanced nodule. Diagnosis was splenic hemangioma.
Patient with suspected HL relapse in the liver, post-bone marrow transplantation

Nonenhanced harmonic compound US shows 1 cm nodule in the liver (V seg)

FDG PET/CT scan
Perfusion phase contrast-enhanced US shows the rim-enhancement of the nodule.

Diagnosis: micotic abscess (biopsy-proven)
Nonenhanced harmonic compound US shows a 3-cm nodule.

Color-Doppler examination

Staging in a patient with HL: focus on spleen (FDG PET+)

Arterial phase contrast-enhanced US shows an isoechoic and isoenhanced nodule. Parenchymal phase contrast-enhanced US shows a clear hypoechoic defect in the nodule.

Diagnosis: nodular infiltration in the spleen by HL (biopsy-proven)
ROI = I / T
Red-line = Hodgkin lymphoma / Yellow-line = normal tissue
Issue 3: What is the best imaging tool to characterize the nodules in the spleen?

Contrast-enhanced Harmonic Compound US of the Spleen to Increase Staging Accuracy in Patients with Hodgkin Lymphoma: A Prospective Study

Picardi M et al. Radiology 2009; 251: 574-582
Aim of the study
To prospectively compare the efficacy of contrast-enhanced US, diagnostic CT (with hepatic arterial and portal venous phases, at 30 and 60 seconds after contrast injection) and FDG PET (with nonenhanced low-dose CT for segmented attenuation correction) in detecting nodular infiltration in the spleen of patients with newly diagnosed HL, at pre-treatment staging.

Picardi M et al. Radiology 2009; 251: 574-582
According to the Reference Standard*: Overall 30/100 patients had splenic nodular infiltrations

Sensitivity rates:
- Perfusion US 100% (30/30 nodular infiltrations)
- FDG PET 43% (13/30 nodular infiltrations)
- Perfusion CT 43% (13/30 nodular infiltrations)

False-negative rates:
- FDG PET 57%
- Perfusion CT 57%

*Picardi M et al. Radiology 2009; 251: 574-582
13 patients were upstaged, moving from an originally limited disease (stage I and stage II with only supradiaphragmatic involvement) to a more extended disease (stage III s with supradiaphragmatic and splenic involvement)

**Table 2**

<table>
<thead>
<tr>
<th>Conventional Staging</th>
<th>I</th>
<th>II</th>
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<th>III s</th>
<th>IV</th>
<th>IV s</th>
<th>Total</th>
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<tbody>
<tr>
<td>I</td>
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<td>III</td>
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<tr>
<td>Total</td>
<td>7</td>
<td>52</td>
<td>7</td>
<td>26</td>
<td>4</td>
<td>4</td>
<td>100</td>
</tr>
</tbody>
</table>

Note.—Data are the number of patients.

Picardi M et al. Radiology 2009; 251: 574-582
The best imaging tool to detect splenic nodular involvement by HL!

Report of a Committee Convened To Discuss the Evaluation and Staging of Patients with Hodgkin’s Disease: Cotswolds Meeting

By T.A. Lister, D. Crowther, S.B. Sutcliffe, E. Glatstein, G.P. Canellos, R.C. Young, S.A. Rosenberg, C.A. Coltman, and M. Tubiana

The Ann Arbor classification for describing the stage of Hodgkin’s disease at initial presentation has formed the basis upon which treatment is selected and has allowed comparison of results achieved by different investigators for almost two decades. A meeting was convened to review the classification and modify it in the light of experience gained in its use and new techniques for evaluating disease. It was concluded that the structure of the classification be maintained. It was particularly recommended: (1) that computed tomography (CT) be included as a technique for evaluating intrathoracic and infradiaphragmatic lymph nodes; (2) that the criteria for clinical involvement of the spleen and liver be modified to include evidence of focal defects with two imaging techniques and that abnormalities of liver function be ignored; (3) that the suffix ‘X’ to designate bulky disease (greater than 10 cm maximum dimension) be introduced; and (4) that a new category of response to therapy, unconfirmed/uncertain complete remission (CR[u]), be introduced to accommodate the difficulty of persistent radiological abnormalities of uncertain significance.

Fused FDG PET/contrast-enhanced CT as a single front-line imaging tool to stage and to guide treatment strategy

Fused FDG–PET/contrast-enhanced CT detects occult subdiaphragmatic involvement of Hodgkin’s lymphoma thereby identifying patients requiring six cycles of anthracycline-containing chemotherapy and consolidation radiation of spleen

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Efficacy of a combined treatment strategy

**Historical cohort**
(patients staged with separate PET and diagnostic CT acquisitions)

- Pretreatment staging: 132 consecutive newly diagnosed HL patients from 2004 to 2006
  - Contraindication to contrast agent injection, n=8 *
    - Reduction of treatment schedule for co-morbidities (n=10) or acute toxicity (n=4) **
    - Lost to post-treatment follow-up, n=10

  - Analyzed patients, n=100
  - Median follow-up 29 months (range, 11-36 months)

**Fused PET/CT group**

- Pretreatment staging: 133 consecutive newly diagnosed HL patients from 2007 to 2009
  - Contraindication to contrast agent injection, n=10 *
    - Reduction of treatment schedule for co-morbidities (n=10) or acute toxicity (n=3) **
    - Lost to post-treatment follow-up, n=7

  - Analyzed patients, n=103
  - Median follow-up 26 months (range, 13-32 months)

* These patients did not receive study treatment strategy
** Nine of these 14 patients did not achieve complete remission at the end of treatment
* These patients did not receive study treatment strategy
** Seven of these 13 patients did not achieve complete remission at the end of treatment
Table 2. Difference in staging between the two series of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fused PET/CT group ( n = 103 )</th>
<th>Historical cohort ( n = 100 )</th>
<th>( P )</th>
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<tr>
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<td>IV</td>
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<td>Subdiaphragmatic lymph node</td>
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<td>involvement</td>
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<td>Spleen involvement</td>
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<td>14</td>
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<td>Extranodal disease</td>
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<tr>
<td>Liver</td>
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<td>Bone</td>
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<td>NS</td>
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<tr>
<td>Lung</td>
<td>10</td>
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<tr>
<td>International prognostic index(^a)</td>
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<td>0–1</td>
<td>13</td>
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<td>4–7</td>
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\(^a\)Patients with unknown risk factor values have been included in the calculation of the International Prognostic Index (IPI).
Figure 3. Splenic lymphoma nodule, as revealed by fused PET/contrast-enhanced CT: (A) a subcentimeter nodular hypodensity in respect to the surrounding tissue during the portal phase of perfusion study at CT, (B) FDG focal uptake at PET scans, and (C) imaging of fusion of the nodule. Liver lymphoma nodule, as revealed by fused PET/contrast-enhanced CT: (D) a centimeter nodular hypodensity in respect to the surrounding tissue during the portal phase of perfusion study at CT, (E) FDG focal uptake at PET scans, and (F) imaging of fusion of the nodule. CT, computed tomography; FDG-PET, 2-[fluorine-18]fluoro-2-deoxy-d-glucose--positron emission tomography.
Table 3. Chemotherapy and radiotherapy received according to pretreatment staging

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Chemotherapy No. of cycles of VEBEP</th>
<th>Irradiated fields</th>
<th>Residual mass</th>
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<td>Mantle</td>
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<td>Subdiaphragmatic</td>
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<td>Para-aortics</td>
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<td>Historical cohort</td>
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<td>70</td>
<td>10</td>
<td>8</td>
<td>25</td>
<td>17</td>
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<tr>
<td>Advanced stage</td>
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<td>–</td>
<td>6</td>
<td>30</td>
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<td>Fused PET/CT group</td>
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<tr>
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<td>58</td>
<td>8</td>
<td>6</td>
<td>22</td>
<td>15</td>
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<tr>
<td>Advanced stage</td>
<td>45</td>
<td>–</td>
<td>4</td>
<td>30</td>
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</tbody>
</table>

Data are the numbers of patients. VEBEP is the induction chemotherapy regimen used in the study (see text). T-field: irradiation of low neck and mediastinum; mantle: irradiation of the lymph node sites above the diaphragm; inverted Y: irradiation of para-aortic and pelvic lymph nodes; residual mass: irradiation of residual nodes at the initial bulky sites; spleen area: irradiation of spleen plus splenic hilar region in cases of pretreatment massive spleen involvement.

*These patients after the completion of the six courses of chemotherapy underwent observation without further therapy.

CT, computed tomography; PET, 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography.
In conclusion

We should use integrated imaging (at least two techniques supported by i.v. contrast agents) to detect spleen invasion in patients with Hodgkin lymphoma.
Thank you for your attention

Naples, Italy