International Workshop for PET in Lymphoma Staging and Restaging
Thursday October 4th, Menton.

Staging: Recommendations for bone marrow investigations

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Hodgkin lymphoma – existing recommendations

- **Cotswolds:** Routine BMB restricted to patients with CT-assessed stage III/IV disease or stage II disease with adverse factors and only if a positive finding would alter the treatment plan[1]
- **ESMO guidelines:** Bone marrow aspirate and biopsy for all patients[2]
- **NCCN Guidelines:** Adequate bone marrow biopsy in stage IB, 2B and stage III-IV
- **Italian recommendations:** Monolateral bone marrow biopsy should be performed in patients with B symptoms and/or stage III/IV disease and/or blood count abnormalities[3]

[1] Lister et al. J Clin Oncol 1989; 7(11): 1630-6.
[2] Eichenauer et al. Ann Oncol 2011; 22(suppl 6): vi55-vi58.
[3] Brusamolino et al. Haematologica 2009; 94(4): 550–565.

Hodgkin lymphoma

- BM involvement is rare in otherwise localised HL: 50/955 patients had positive BMT and 5/955 had positive BMA[1]
- Several predictive algoriths have been proposed, based on clinical and radiological examinations, histology and, and lab values. However, they have not come into widespread use[2,3]
- After the introduction of PET/CT staging, the use of routine staging BMB has decreased. According to a recent UK study, only 30% of centres use routine BMB for all HL patients, this number is 70% for centres without PET/CT[4]

[1] Howell et al. Br J Haematol 2002; 119: 408– 411.
[2] Vassilakopoulos et al. Blood 2005; 105(5): 1875-80.
[3] Levis et al. Clin Lymphoma 2004; 5(1): 50-5.
[4] Richardson et al. Leuk Lymphoma 2012; 53: 381–385.

Hodgkin lymphoma

- 83 HL patients: Focal skeletal PET/CT lesions in all patients with positive BMB (n=7). Focal skeletal PET/CT lesions were also found in 11 patients in whom BMB was without signs of HL and MRI studies suggested bone alterations consistent with lymphoma in three of these patients[1]
- In eight other studies covering a total of 816 HL patients, including 175 pediatric cases, only nine cases of BM involvement were missed by PET based imaging[2-9]

[1] Moulin-Romsee et al. EJNM 2010; 37(6): 1095-105.
[2] Rigacci et al. Ann Hematol 2007; 86(12): 897-903.
[3] Naumann et al. Br J Cancer 2004; 90(3): 620-5.
[4] Pelosi et al. Q J Nucl Med Mol Imaging 2011; 55(4): 469-75.
[5] Jerusalem et al. Haematologica 2001; 86(3): 266-73.
[6] Elstrom et al. Blood 2003; 101(10): 3875-6.
[7] Purz et al. J Clin Oncol 2011; 29(26): 3523-8.
[8] Richardson et al. Leuk Lymphoma 2012; 53: 381–385.
[9] Muzahir et al. Br J Radiol 2012;85(1016): e490-6.

Hodgkin lymphoma

- 454 Danish Hodgkin lymphoma patients with BMB and staging PET/CT
- 82 (18%) had focal skeletal PET/CT lesions
- 27 (6%) had positive BMB
- No patients with positive BMB were assessed as having stage I-II disease by PET/CT staging
- BMB upstaged five patients, assessed as being stage III prior to BMB
- None of the 454 patients would have been allocated to another treatment or risk group on the basis of BMB results

El-Galaly et al. J Clin Oncol, in press.

Diffuse large B-cell lymphoma – existing guidelines

- **ESMO guidelines:** Bone marrow aspirate and biopsy for all patients with a curative treatment intent[1]
- **NCCN Guidelines:** Adequate bone marrow biopsy and aspirate in all patients

[1] Tilly et al. Ann Oncol 2010; 21(suppl 5): v172-v174.

Diffuse large B-cell lymphoma

- BM involvement is more common in DLBCL than in HL
- Histology of BM involvement is also more important than in HL, because patients with concordant (aggressive) BM involvement have a worse prognosis than patients with discordant (indolent) BM involvement[1]
- A number of studies have shown a high PPV in the diagnosis of BM involvement[2,3]

[1] Sehn et al. J Clin Oncol 2011; 29(11): 1452-7.
[2] Elstrom et al. Blood 2003;101(10):3875-6.
[3] Pakos et al. J Nucl Med 2005;46(6):958-63.

Diffuse large B-cell lymphoma

- 89 DLBCL patients: 14 with positive BMB, and 17 with positive BM PET/CT
  - 17 patients had a discordant interpretation (seven patients were BMB+ and FDG-PET/CT−, and 7 were BMB− and FDG-PET/CT+)
  - BMB+ patients had an inferior 2-year EFS compared to BMB− patients, but there was no significant difference in EFS between FDG-PET/CT+ and FDG-PET/CT− patients
  - Six of 7 patients with diffuse hypermetabolism were BMB+, only 1 of 10 patients with focal hypermetabolism was BMB+.
  - FDG-PET/CT had a limited value to detect BM involvement in patients with DLBCL

Hong et al. Ann Hematol 2012; 91(5): 687-95.

Diffuse large B-cell lymphoma

- PET finds BM involvement not detected by BMB:
  - In a Chinese study of 81 DLBCL patients, 23 were diagnosed as BM involvement by PET/CT. Of the 23 positive cases 17 were confirmed by biopsy (11 by bilateral iliac crest biopsy, the rest by PET/CT directed BM biopsy)[1]
- On the other hand, BM involvement occurs in patients with with PET-negatives bones:
  - Zelenetz et al: Retrospective study of > 1300 lymphoma cases: 13.5% of patients with DLBCL had a positive BM despite BM negative PET/CT[2]

[1] Zhang et al. Zhonhua Xue Ye Xue Za Zhi. 2008;29(12):832-5.
[2] Zelenetz et al. Blood 2011; 118: 2640.

Other types of NHL

- PET/CT has a high sensitivity for extranodal disease in most lymphoma subtypes
- The role of PET/CT vs. BMB has not been studied in large series
- According to the recent MSKCC survey, 35% of patients with FL had a positive BM despite BM negative PET/CT[2]

- **There are no data to support the omission of BMB in PET/CT staged lymphoma patients with other histologies than HL and DLBCL**

[2] Zelenetz et al. Blood 2011; 118: 2640.

Recommendation A

- **In HL staged by PET-CT there is no role for routine BMB. BMB is indicated only for confirmation if there is unexpected marrow involvement on PET in early good prognosis disease (*category 1*).**
- **In DLBCL, if PET suggests BM involvement, this could obviate the need for BMB as PET-CT has a high positive predictive value. In the absence of abnormal marrow uptake on PET, BMB may be indicated to detect a small proportion of patients with low volume marrow involvement where it would influence prognosis and/or treatment. (*category 1*).**

Recommendation B

- **In HL and DLBCL staged by PET-CT there is no role for routine BMB. BMB is indicated only if it would change staging with a resultant change in therapy *(category 1)***