Opportunities and limitations of bone marrow biopsy and bone marrow FDG-PET in lymphoma

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1. Introduction

The bone marrow is an important anatomical site where lymphomatous cells can reside. Detection of lymphomatous bone marrow involvement may be clinically relevant from several perspectives. First, identifying lymphomatous cells in the bone marrow may aid in the diagnosis of lymphoma if extramedullary sites are not available or not accessible for histopathological examination. Second, bone marrow assessment is a crucial part of the Ann Arbor system, which is the most commonly used staging tool in lymphoma, and in which bone marrow involvement implies the highest disease stage (stage IV) [1–3]. Bone marrow involvement is, either directly or indirectly through the Ann Arbor system, also an important factor in most clinical risk stratification indices, including the International Prognostic Score (IPS) for advanced Hodgkin lymphoma [4], the International Prognostic Index (IPI) and its successors for aggressive non-Hodgkin lymphoma and diffuse large B-cell lymphoma (DLBCL) [5–7], and the Follicular Lymphoma International Prognostic Index (FLIPI) and new FLIPI 2 for follicular lymphoma [8,9]. Importantly, it should be realized that these clinical risk stratification indices only used lymphoma-positive bone marrow biopsy (BMB) specimens as proof of bone marrow involvement [4–8], and not bone marrow involvement as detected by 18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET). Third, the presence of bone marrow involvement may change the choice of therapy, particularly in patients who were thought to have early stage disease only before bone marrow evaluation. Fourth, bone marrow involvement has been reported to be an important predictor of occurrence of an infusion-related reaction following rituximab administration [10]. Fifth, knowing all sites of lymphomatous involvement, including bone marrow sites, allows monitoring the effects of therapy [11].

BMB has been the established method for bone marrow evaluation in various diseases, including lymphoma, for many decades [12,13]. Meanwhile, FDG-PET has become an established method for lymphoma staging, and it may potentially be a non-invasive alternative or complementary method to BMB. However, its clinical value in the evaluation of the bone marrow in lymphoma is still under debate and investigation. The purpose of this scientific communication is to provide an evidence-based overview about the opportunities and limitations of BMB and FDG-PET in the evaluation of the bone marrow in patients with lymphoma. This article first reviews the basic properties, opportunities and limitations of BMB and bone marrow FDG-PET, and then focuses on the clinical utility of BMB and bone marrow FDG-PET in three major lymphoma subtypes including Hodgkin lymphoma, diffuse large B-cell lymphoma, and follicular lymphoma.
extramedullary sites, which has been reported to occur most frequently in follicular lymphoma and DLBCL [14,15]. BMB may also be useful in establishing the diagnosis of lymphoma if histologic examination of extramedullary tissue is inconclusive or not possible. Finally, histologic examination of the bone marrow may incidentally result in the diagnosis of another, non-lymphoma bone marrow disease.

One major disadvantage of BMB is its invasiveness. It is a stressful and painful procedure, despite the use of local anesthesia. In a series of 235 adult patients, about 70% of patients experienced procedure-related pain, with one-third of these patients indicating severe pain [16]. Sedation with drugs such as lorazepam, midazolam or diazepam is often administered in addition to local anesthesia, which has been reported to reduce anxiety, pain perception and result in retrograde amnesia for the procedure in many patients [17–19]. However, apart from these beneficial effects, performing BMB under sedation has drawbacks, like requirement of additional staff and equipment and prolongation of hospital stay. In a series of 19,259 procedures from 63 hospitals, with 13,147 being a combination of bone marrow aspiration and trephine biopsy and 6112 aspirates without trephine biopsy, 16 adverse events were reported, representing 0.08% of total reported procedures [20]. The major adverse event was hemorrhage, which comprised 11 of the 16 adverse events [20]. Although infrequent, adverse events were associated with significant morbidity and three were judged as very serious [20]. Another major shortcoming is that BMB assesses only a very small portion of the entire bone marrow, as a result of which focal bone marrow involvement may be missed (Fig. 1). This has been demonstrated by previous studies in which bilateral or paired ipsilateral BMBs were performed in the same patients, and in which only one bone marrow specimen was positive for lymphoma in a considerable proportion of patients, ranging between 10–60% [21–24].

Obtaining multiple tissue samples from different locations improves the diagnostic yield of BMB [21–24], but obviously increases patient burden and complication rate. Due to the risk of sampling errors, it should be realized that a negative BMB after completion of therapy cannot reliably exclude residual bone marrow involvement either. The suboptimal sensitivity of BMB also indicates the need to carefully interpret previously reported BMB-based incidences of bone marrow involvement in different lymphoma subtypes, since these percentages are underestimated. It also underlines the importance of refraining from using BMB as reference standard in imaging studies to calculate false positives and true negatives on a patient level, because a negative BMB does not exclude bone marrow involvement [25]. Yet another disadvantage of BMB is that marrow tissue should be fixed and decalcified before it can be histologically examined [26], which is a time-consuming procedure that may cause delay in diagnostic workup and postponement of treatment initiation. The aforementioned disadvantages of BMB show the importance of refraining from performing a BMB in patients who are at very low risk of having bone marrow involvement (based on epidemiological data, clinical prediction rules, or imaging techniques) or in patients in whom the bone marrow result will not have any (therapeutic) consequences.

3. Bone marrow FDG-PET

Malignant lesions of Hodgkin lymphoma and aggressive lymphomas located outside the bone marrow are generally FDG-avid, and most indolent lymphomas also demonstrate an increased FDG uptake [27]. Therefore, FDG-PET has been proposed as a potentially useful method for bone marrow assessment in lymphoma. A major advantage of FDG-PET is that it allows visualization of the entire marrow, whereas bone marrow assessment by BMB is restricted to the iliac crest/site of biopsy (Fig. 1). Under normal conditions the bone marrow shows homogeneously low uptake of FDG, with the bone marrow appearing less intense than the liver [28]. The distribution of FDG throughout the skeleton follows that of the red marrow [29,30], which changes during normal aging [29–31]. There are no prospectively validated criteria for assessing lymphomatous bone marrow lesions at FDG-PET. The most previously reported studies on this topic consider focal bone marrow FDG uptake exceeding liver FDG uptake as indicative of bone marrow involvement [32,33]. This criterion is also reported in the recently published Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma [34,35], whereas less consensus has been reached on the interpretation of homogeneously, diffusely increased bone marrow FDG uptake [34–39] (see the later section). Unfortunately, the determination of the actual diagnostic value of bone marrow FDG-PET is difficult, since studies that perform FDG-PET guided targeted biopsies are scarce and often only iliac crest BMBs are available for confirmation. However, lesions located outside the iliac crest will be missed by BMB, which will erroneously result in false-positive and true-negative bone marrow FDG-PET cases if only BMB is used as reference standard [25]. In other words, BMB is not a suitable reference standard to calculate the specificity of bone marrow FDG-PET at a patient level. Multiple studies have tried to overcome this problem by using follow-up FDG-PET scans as part of their reference standard and considering FDG-avid bone marrow lesions at baseline as true-positive when these lesions disappear during or after therapy. However, benign bone marrow lesions and even active physiological red marrow may also show (either focally or diffusely) increased bone marrow FDG uptake that can decline after therapy [36,40–46]. Thus, follow-up FDG-PET examinations may not be reliable for this purpose.

4. Hodgkin lymphoma

4.1. BMB

Bone marrow involvement is rare in Hodgkin lymphoma, with a BMB-based incidence varying between 4% and 14% [47,48]. In clinical/radiological stage IA or IIA disease (without taking into account BMB results), the incidence of bone marrow involvement has been reported to be even lower or close to, if not, 0% [48]. In line with the low incidence of bone marrow involvement in this disease, the Cotswolds report on the evaluation and staging of Hodgkin lymphoma that was issued in 1989 (far before FDG-PET was routinely implemented in clinical practice), already recommended to restrict BMB to patients with computed
tomography (CT)-based stage III/IV disease or stage II disease with adverse unfavorable factors, and only if a positive finding would change treatment planning [49]. Prediction rules have been developed to estimate the risk of bone marrow involvement, in order to avoid BMB in certain subgroups of patients. Based on a series of 826 Hodgkin lymphoma patients, enhanced with a validation group of another 654 patients, it was reported that patients with low risk (stage I/IIA without anemia and leukopenia; stage IA/IIA, younger than 35 years, with either anemia or leukopenia but no inguinal/iliac involvement; and stage IIA/IVA without any of these four risk factors) do not require BMB [47]. Thus, even without the use of bone marrow FDG-PET, the correlation between clinical/radiological Ann Arbor stage and the prevalence of BMB-proven bone marrow involvement, and the availability of efficient clinical prediction rules allowing sparing BMB in many Hodgkin lymphoma patients. Nevertheless, at least until recently, there was still a lot of variation with regard to the use or omission of BMB in Hodgkin lymphoma patients in routine clinical practice [50].

Of interest, BMB-based lymphomatous involvement has not been proven to be a major adverse predictor of outcome in Hodgkin lymphoma. In the cohort on the development of the IPS in advanced stage Hodgkin lymphoma, progression-free survival (PFS) and overall survival (OS) in 614 patients with BMB-proven bone marrow involvement (60% and 70%, respectively) were not significantly different from those in 1351 patients without bone marrow involvement according to BMB (61% and 74%, respectively) [4]. This indicates that omission of BMB will not result in a major decline in prognostic power of the IPS in patients with advanced stage disease [4]. In early stage disease, the incidence of bone marrow involvement is extremely low, and the prognostic value of BMB in this subpopulation has therefore not been well documented.

4.2. Bone marrow FDG-PET

FDG-PET is much more frequently positive for bone marrow involvement than BMB in patients with Hodgkin lymphoma (Table 1), and has therefore been proposed as a very sensitive method for the detection of bone marrow involvement that may surpass the diagnostic yield of BMB [34,35]. However, multiple studies have shown that there is a considerable proportion of Hodgkin lymphoma patients with a positive BMB do not have pathological FDG uptake in the bone marrow (Table 1). Nevertheless, current guidelines do not recommend to routinely perform BMB in all patients [34,35,51]. Regardless of the sensitivity of bone marrow FDG-PET, it is more important to consider the therapeutic consequences of omitting BMB in patients who actually have lymphomatous bone marrow involvement. El-Galaly et al. [52] included 454 Hodgkin lymphoma patients and reported that BMB did not change treatment planning in their series since no positive BMFs in FDG-PET/CT-assessed stage I–II disease were observed. It should be noted that positive BMFs are also rarely found in CT-based stage I–II disease [48,49]. Therefore, it is unlikely that bone marrow FDG-PET will have any substantial additional value in terms of treatment consequences in patients who have already undergone either FDG-PET/CT or CT only for extramedullary staging.

Data on the prognostic impact of bone marrow FDG-PET in Hodgkin lymphoma are scarce. El-Galaly reported that in a group of 414 cases, patients with skeletal lesions at FDG-PET had significantly worse PFS and OS (63% and 77%, respectively) than those without (85% and 91%, respectively). However, on multivariate analysis, FDG-PET-based bone marrow involvement was not an independent predictor of outcome after correcting for the risk factors age ≥ 45 years and Eastern Cooperative Oncology Group performance score ≥ 2. Bone marrow FDG-PET/CT findings are not incorporated in any current risk stratification index for Hodgkin lymphoma, including the IPS for advanced Hodgkin lymphoma [4].

5. DLBCL

5.1. BMB

DLBCL has a reported BMB-based incidence of bone marrow involvement of around 11–17% [53–55]. In early stage DLBCL (i.e. stage I–II disease), this incidence drops to 3.6% [56]. In a study of 120 patients with early stage DLBCL who had normal hemoglobin levels, normal white blood cell count, and no bulky disease, only one patient (0.83%) had bone marrow involvement [56]. The absence of all three factors yielded a negative predictive value of 99.2% [56]. These results suggest that BMB may safely be omitted in selected patients with early stage DLBCL [56]. In another series of 113 DLBCL patients, 0 of 17 patients (0%) with stage I disease had a positive BMB, 1 of 10 patients (10%) with stage II disease had a positive BMB, 6 of 27 patients (22.2%) with stage III disease had a positive BMB, and 11 of 59 patients (18.6%) with stage IV disease had a positive BMB [57], which confirms the need to reconsider the need for routine BMB in early stage disease. In the same study, BMB findings changed the National Comprehensive Cancer Network (NCCN) [7] (which is the best validated risk stratification model in DLBCL that is treated with rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone [R-CHOP]) in 9 of 113 patients (8.0%) [57]. Five patients were upstaged from low-intermediate to high-intermediate risk, and four patients were upstaged from high-intermediate to high risk. However, BMB findings changed treatment planning in none of the 113 patients. These findings support the omission of BMB from routine staging of newly diagnosed DLBCL in the current risk stratification and treatment era, even when bone marrow FDG-PET is not performed [57]. Performing repeat BMBS at the end of treatment in DLBCL patients with bone marrow involvement at baseline is recommended by current guidelines [11,35,58]. However, its additional value in this setting is likely to be low, since a recent study showed that only 1 of 34 (2.9%) patients with lymphoma-positive BMBS at baseline had residual lymphomatous deposits in the BMB after treatment [59]. Other than lymphoma detection, BMB with subsequent histologic examination may also characterize lymphoma cells in the bone marrow. Lymphoma cells in the bone marrow in DLBCL patients can be

Table 1

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. of patients included</th>
<th>No. of patients BMB+</th>
<th>No. of patients FDG-PET+ (%)</th>
<th>Sensitivity of focally increased bone marrow FDG uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiler-Sagie et al. [72] (2014)</td>
<td>330</td>
<td>9 (2.7%)</td>
<td>57 (17.3%)</td>
<td>7/9 (77.8%)</td>
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<td>Cortés-Romera et al. [73] (2013)</td>
<td>63</td>
<td>6 (9.5%)</td>
<td>15 (23.8%)</td>
<td>6/6 (100%)</td>
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<td>Agrawal et al. [74] (2013)</td>
<td>31</td>
<td>5 (16.1%)</td>
<td>7 (22.6%)</td>
<td>4/5 (80%)</td>
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<td>Muzahir et al. [75] (2012)</td>
<td>122</td>
<td>11 (9.0%)</td>
<td>26 (21.3%)</td>
<td>9/11 (81.8%)</td>
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<td>El-Galaly et al. [52] (2012)</td>
<td>454</td>
<td>27 (5.9%)</td>
<td>82 (18.1%)</td>
<td>23/27 (85.2%)</td>
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<td>Pelosi et al. [76] (2011)</td>
<td>82</td>
<td>6 (7.3%)</td>
<td>22 (26.8%)</td>
<td>6/12 (50%)</td>
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<td>Mittal et al. [77] (2011)</td>
<td>20</td>
<td>2 (10%)</td>
<td>5 (25%)</td>
<td>2/2 (100%)</td>
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<td>Cheng et al. [78] (2011)</td>
<td>31</td>
<td>2 (6.5%)</td>
<td>4 (12.9%)</td>
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<td>Moulin-Romero et al. [79] (2010)</td>
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<td>7 (8.4%)</td>
<td>11 (13.3%)</td>
<td>7/7 (100%)</td>
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<td>Ngew et al. [80] (2009)</td>
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<td>1 (4.8%)</td>
<td>3 (14.3%)</td>
<td>1/1 (100%)</td>
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</table>

* Patients with diffusely increased bone marrow FDG uptake were considered negative for bone marrow involvement in Hodgkin lymphoma.
characterized as large cells (i.e. discordant bone marrow involvement) or as small cells (i.e. discordant bone marrow involvement). Importantly, previous studies have shown that discordant bone marrow involvement is an independent and strong predictor of worse outcome, while the prognosis of patients with discordant bone marrow involvement nearly equals that of patients without bone marrow involvement [15, 54,55,60].

5.2. Bone marrow FDG-PET

Although the incidence of BMB-based bone marrow involvement is relatively low in DLBCL [53–56,60], bone marrow involvement according to FDG-PET is relatively common, with a reported incidence between 24–29% in the majority of studies (Table 2). This has resulted in the notion that FDG-PET may have a high sensitivity for the detection of bone marrow involvement in DLBCL, surpassing that of BMB [37]. Consequently, the recently published Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma stated that focal bone marrow FDG uptake is highly sensitive for lymphomatous bone marrow involvement in aggressive lymphoma, including DLBCL, and may obviate the need for BMB [34,35]. However, the actual sensitivity of FDG-PET for diagnosing bone marrow involvement is currently under debate and is highly influenced by the criteria used for the definition of bone marrow involvement. A recent meta-analysis on the diagnostic value of FDG-PET for detecting bone marrow involvement in DLBCL reported high sensitivity and specificity for FDG-PET ranging from 70.8% to 95.8% and 99.0%–100%, with pooled estimates of 88.7% and 99.8% respectively [33]. The studies included in that meta-analysis used both BMB and decrease/disappearance of bone marrow FDG uptake on follow-up FDG-PET scans as proof of bone marrow involvement, but the latter may not be sufficient proof of bone marrow involvement at baseline, as discussed previously. Therefore, the actual diagnostic value of bone marrow FDG-PET is likely to be lower in DLBCL. When only the iliac crest BMB is used as reference standard (without using follow-up FDG-PET scans), the sensitivity of FDG-PET decreases to 50–93.8% when both focally and diffusely increased bone marrow FDG uptake are regarded as positive for bone marrow involvement, and to 43.8–75% if only focally increased bone marrow FDG uptake is regarded as positive for bone marrow involvement (Table 2). Importantly, in all these studies, BMB of the iliac crest was used as reference standard for the assessment of the sensitivity of bone marrow FDG-PET at a patient level. When a spatially matched correlation is performed, i.e. a direct comparison between FDG-PET and BMB findings at the iliac crest, the sensitivity of bone marrow FDG-

<table>
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<tr>
<th>Study (year)</th>
<th>No. of patients included</th>
<th>No. of patients BMB+ (%)</th>
<th>No. of patients FDG-PET+</th>
<th>No. of patients with diffusely increased FDG uptake</th>
<th>Sensitivity of focally and diffusely increased bone marrow FDG uptake</th>
<th>Sensitivity of focally increased bone marrow FDG uptake</th>
<th>Significant adverse prognosis BMB+ vs. BMB+</th>
<th>Significant adverse prognosis FDG-PET+ vs. FDG-PET+</th>
<th>Histopathological characteristics of BMB+− missed by FDG-PET</th>
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<tr>
<td>Cerchi et al. [39] (2014)</td>
<td>327</td>
<td>35 (10.7%)</td>
<td>86 (26.3%)</td>
<td>18</td>
<td>25/35 (71.4%)</td>
<td>21/35 (60.0%)</td>
<td>Yes</td>
<td>NR, but unlikely</td>
<td>6× large-cell involvement &lt;10%</td>
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<td>Adams et al. [62] (2014)</td>
<td>78</td>
<td>16 (20.5%)</td>
<td>34 (43.6%)</td>
<td>4</td>
<td>11/16 (68.8%)</td>
<td>7/16 (43.8%)</td>
<td>Yes</td>
<td>No</td>
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<td>Cortés-Romera et al. [73] (2014)</td>
<td>84</td>
<td>16 (19.0%)</td>
<td>24 (28.8%)</td>
<td>4</td>
<td>15/16 (93.8%)</td>
<td>11/16 (68.8%)</td>
<td>NR</td>
<td>NR</td>
<td>2× small-cell involvement (3% and 20%)</td>
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<tr>
<td>Khan et al. [37] (2013)</td>
<td>130</td>
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<td>33 (25.4%)</td>
<td>2</td>
<td>12/14 (85.7%)</td>
<td>10/14 (71.4%)</td>
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<td>Berthet et al. [38] (2013)</td>
<td>133</td>
<td>8 (6.0%)</td>
<td>32 (24.1%)</td>
<td>11</td>
<td>6/8 (75%)</td>
<td>6/8 (75%)</td>
<td>Yes</td>
<td>Yes</td>
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<td>Hong et al. [63] (2013)</td>
<td>89</td>
<td>14 (15.7%)</td>
<td>17 (19.1%)</td>
<td>NR†</td>
<td>7/14 (50%)</td>
<td>NR†</td>
<td>Yes</td>
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<td>Ngeow et al. [80] (2009)</td>
<td>55</td>
<td>6 (10.9%)</td>
<td>5 (9.1%)</td>
<td>NR</td>
<td>3/6 (50%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1× small cell involvement</td>
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<tr>
<td>Ribrag et al. [81] (2008)</td>
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<td>8 (18.6%)</td>
<td>0</td>
<td>4/5 (80%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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Notes:
+ Positive.
− Negative.
Abbreviations:
NR: Not reported.
† Focally and diffusely increased bone marrow FDG uptake were considered positive at FDG-PET.
‡ At univariate analysis.
§ This study used an alternative definition of diffuse bone marrow FDG uptake, namely: heterogeneously widespread uptake in hematopoietic bone marrow or bony sites with three or more definitely hypermetabolic areas.
PET has been reported to be as low as 14.3% [61]. Of note, studies have also shown that both large-cell (concordant) and small-cell (discordant) bone marrow involvement can be missed by FDG-PET (Table 2).

Another important topic is that although it has been proven that patients with BMB-based bone marrow involvement have a considerably worse outcome [54,60], this does not apply to FDG-PET-based bone marrow involvement. Of the four published studies on the prognostic value of bone marrow FDG-PET in DLBCL [37,38,62,63], three reported that FDG-PET-based bone marrow involvement does not have any prognostic value at all [37,62,63]. The only study that reported FDG-PET-based bone marrow involvement to have prognostic value clearly showed that bone marrow FDG-PET was prognostically inferior to BMB [38]. That particular study reported bone marrow FDG-PET negative patients to have 2-year PFS and OS of 84.5% and 88.5%, and bone marrow FDG-PET positive patients to have PFS and OS of 62.5% and 76.1%, respectively [38]. However, the 2-year PFS and OS of BMB-negative patients were 82.1% and 87.2%, and those of BMB-positive patients were 37.5% and 62.5%, respectively, which clearly shows that BMB is better at selecting patients with a worse prognosis [38]. It has been speculated that the absent or weak prognostic implications of bone marrow FDG-PET may be due to the detection of small and prognostically irrelevant lymphoma deposits, in contrast to BMB that is more likely to be positive only in the case of extensive marrow involvement [64]. However, it has recently been proven that quantification of the (metabolic) volume of bone marrow lesions at FDG-PET does not improve prognostication either [44]. FDG-PET-based bone marrow involvement has not been incorporated in the recently improved (National Comprehensive Cancer Network) IPI, and this prognostic index explicitly states that only histologically established bone marrow involvement, and not imaging-based bone marrow involvement should be used for risk stratification [7].

6. Follicular lymphoma

6.1. BMB

Bone marrow involvement is very common in follicular lymphoma [65], with up to 50% of patients having a positive BMB [66]. Staging is particularly important in the small proportion of patients with limited non-bulky Ann Arbor stage I–II disease (10–15%), in whom involved-field radiation therapy is the preferred treatment with curative potential provided bone marrow involvement is absent [67]. Therefore, the National Comprehensive Cancer Network guidelines [68] recommend bilateral BMB if curative therapy is considered, but state that BMB may be deferred if observation is the initial therapy. Other guidelines, however, recommend performing unilateral BMB in all patients with follicular lymphoma [34,35,67]. Although rare, BMB results may sometimes reveal involvement by an aggressive lymphoma and consequently result in rapid treatment initiation [14,67]. The prognostic role of positive BMBs in follicular lymphoma is well defined. The cohort that was used for the development of the FLIPI included 4016 patients who underwent BMB. Patients with a positive BMB had a significantly reduced 5-year OS (65.7% vs. 75.6%) and 10-year OS (40.4% vs. 56.2%) compared to patients with a negative BMB [8]. Bone marrow involvement remained an independent predictor of outcome in the multivariate analysis (P = 0.001) and was therefore incorporated into the FLIPI [8]. Similar results were observed in the cohort of the FLIPI 2 study which included 832 patients and showed that bone marrow status was an independent predictor of outcome, thus justifying the inclusion of BMB findings in that prognostic index [9].

6.2. Bone marrow FDG-PET

In contrast to the high BMB-based incidence of bone marrow involvement, pathologically increased bone marrow FDG uptake has been reported to occur in only 20–25% of follicular lymphoma cases, with a considerable proportion of these cases having diffusely increased bone marrow FDG uptake (Table 3). Unfortunately, the detectability of bone marrow involvement by FDG-PET is low in follicular lymphoma, with reported sensitivities ranging between 20.3–28.9% (Table 3). Thus, bone marrow FDG-PET cannot replace BMB in follicular lymphoma. However, difficulty arises as how to interpret bone marrow involvement according to FDG-PET in patients with a negative BMB. There are currently no studies that evaluated the prognostic potential of bone marrow FDG-PET in follicular lymphoma, and bone marrow FDG-PET findings are not part of the FLIPI or FLIPI 2 [8,69]. Therefore, at present it is controversial to classify patients with positive bone marrow FDG-PET findings as having stage IV disease without histologic proof of bone marrow involvement.

7. Diffusely increased bone marrow FDG uptake

Diffusely increased bone marrow FDG uptake, usually defined as homogeneous FDG uptake of the entire axial skeleton that exceeds liver uptake (Fig. 2), is a well-known phenomenon in patients treated with hematopoietic growth factors following chemotherapy [70,71], but is relatively uncommon in newly diagnosed and recently untreated lymphoma patients [37,39,62]. This particular phenomenon deserves special attention to correctly interpret its clinical relevance. At diagnosis, its incidence has been reported to range between 5.2–9.3% in Hodgkin lymphoma, between 3.8–8.3% in DLBCL, and between 11.1–14.0% in follicular lymphoma (Table 4). In a study of 23 recently untreated lymphoma patients with diffusely increased bone marrow FDG uptake, 91.3% were anemic, 81.0% had elevated C-reactive protein levels, 47.8% had leukocytosis, 39.1% had thrombocytopenia and 21.7% had thrombocytosis [36]. Although the relationship between diffusely increased bone marrow FDG uptake and laboratory alterations suggests that this phenomenon may be related to a reactive bone marrow process or altered blood composition rather than lymphomatous bone marrow involvement, this does not appear to be the case in all lymphoma subtypes. In Hodgkin lymphoma, BMBs of patients with diffusely increased bone marrow FDG uptake are usually negative for lymphoma, but in non-Hodgkin lymphomas these results are not consistent (Table 4). Two of four studies on this topic in DLBCL reported that BMBs of all patients with diffusely increased bone marrow FDG uptake showed lymphomatous involvement [37,62], whereas two other studies on this topic in DLBCL reported BMB to be negative in the majority of these cases [38,39]. Of note, it was not consistently reported in all

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. of patients included</th>
<th>No of patients BMB+</th>
<th>No of patients FDG-PET+</th>
<th>No. of patients with diffusely increased bone marrow FDG uptake</th>
<th>Sensitivity of focally and diffusely increased bone marrow FDG uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminari et al. [69] (2013)</td>
<td>142</td>
<td>70 (49.3%)</td>
<td>34 (23.9%)</td>
<td>NR</td>
<td>24/70 (34.3%)</td>
</tr>
<tr>
<td>Le Dortz et al. [82] (2010)</td>
<td>45</td>
<td>20 (44.4%)</td>
<td>13 (28.9%)</td>
<td>8</td>
<td>8/20 (40%)</td>
</tr>
<tr>
<td>Wohrer et al. [83] (2006)</td>
<td>64</td>
<td>24 (37.5%)</td>
<td>13 (20.3%)</td>
<td>4</td>
<td>13/24 (54.2%)</td>
</tr>
</tbody>
</table>

Abbreviations:
NR: Not reported.
* Focally and diffusely increased FDG-uptake were considered positive at FDG-PET.
studies whether or not therapies such as hematopoietic growth factor administration were used prior to FDG-PET acquisition which could be an explanation for the different results. Moreover, clear criteria to define diffusely increased bone marrow FDG uptake are not yet established, and variability in the interpretation of FDG-PET scans among studies might be another explanation for the discrepant results. In follicular lymphoma, the limited data show that BMBs are positive for lymphoma in the majority of cases with diffusely increased bone marrow FDG uptake (Table 4).

8. Summary

BMB is invasive and provides histologic examination of a small bone marrow sample, whereas FDG-PET is non-invasive and allows visualization of the entire bone marrow but lacks histologic material. Table 5 summarizes the general advantages/applications and disadvantages/limitations of BMB and FDG-PET in the evaluation of the bone marrow. In Hodgkin lymphoma, the combination of the very low incidence of bone marrow involvement in early stage disease, and the lack of treatment consequences if bone marrow involvement is missed in advanced stage disease, allows omitting BMB if a FDG-PET staging examination has been performed. This notion likely also holds true if CT only is performed for staging. In DLBCL, the diagnostic value of FDG-PET to identify patients with involved BMBs is suboptimal and although bone marrow involvement at BMB has been established as an important adverse prognostic factor, the prognostic consequences of bone marrow involvement at FDG-PET are absent. Thus, most evidence suggests that FDG-PET cannot replace BMB. On the other hand, the additional value of BMB to the standard diagnostic work-up in DLBCL is also limited in terms of therapy planning. In follicular lymphoma, FDG-PET is insufficiently sensitive for bone marrow involvement, and BMB remains recommended, particularly when potentially curative therapy is considered. Table 6 summarizes the current evidence-based clinical utility of bone marrow FDG-
PET in Hodgkin lymphoma, DLBCL, and follicular lymphoma. Future studies (for example large-scale studies that perform FDG-PET guided BMBs) are needed to solve existing controversies and to fill in knowledge gaps on the role of bone marrow FDG-PET in lymphoma.

Conflict of interest

The authors declare that there are no conflicts of interest.

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References


Table 6

Current evidence-based clinical utility of BMB and bone marrow FDG-PET in Hodgkin lymphoma, DLBCL, and follicular lymphoma.

<table>
<thead>
<tr>
<th>Hodgkin lymphoma</th>
<th>DLBCL</th>
<th>Follicular lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence bone marrow involvement according to BMB</td>
<td>4–14% [47,48] approaching 0% in clinical stage IA-IIA disease, [48]</td>
<td>11–17% [53,54,60] 3.6% in stage I-II disease</td>
</tr>
<tr>
<td>Therapeutic impact BMB</td>
<td>Absent/negligible</td>
<td>Absent/negligible</td>
</tr>
<tr>
<td>Independent prognostic impact BMB</td>
<td>No/weak [4,84]</td>
<td>– Concordant bone marrow involvement: strong</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Discordant bone marrow involvement: weak [7,54,60]</td>
</tr>
<tr>
<td>Incidence bone marrow involvement according to FDG-PET</td>
<td>12.9–23.8% [6]</td>
<td>Usually 24–29%, reported range: 9.1–43.6%</td>
</tr>
<tr>
<td>BMB necessary according to recent international guidelines?</td>
<td>No [34,35,51]</td>
<td>Debatable, depending on FDG-PET findings and clinical situation [34,35]</td>
</tr>
</tbody>
</table>

a Based on BMB studies.
b See Table 1.
c See Table 2.
d See Table 3.


