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Commentary

Detecting marrow involvement in lymphoma: Can-^{18}F fluorodeoxyglucose positron emission tomography elude the need for biopsy?

Detection of marrow involvement in lymphoma is important as it signifies stage IV disease and has prognostic significance. It is included in the commonly used risk stratification indices such as International Prognostic Score (IPS) for advanced Hodgkin's lymphoma (HL)[1], the International Prognostic Index (IPI) and its successors for aggressive non-HL (NHL) and diffuse large B-cell lymphoma (DLBCL)[2,3], and the Follicular Lymphoma IPI (FLIPI and FLIPI 2) for follicular lymphoma[4,5]. All these indices use bone marrow biopsy (BMB) as proof for marrow involvement. Although BMB has conventionally been used to detect marrow involvement, it is invasive and may cause considerable pain and discomfort to the patient. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET) has emerged as a useful imaging modality for staging lymphomas enabling a simultaneous assessment of marrow alongwith extramedullary sites of disease involvement.

That FDG-PET is considered highly sensitive is intuitive, since it images the whole body whereas BMB samples the marrow from a specific site and is therefore prone to sampling error. BMB from bilateral iliac crests or PET-guided BMB is expected to improve the sensitivity but is not readily feasible in routine clinical practice. In addition, BMB can be painful in a significant proportion of patients despite analgesia[6]. FDG-PET is increasingly being used for staging and response assessment in lymphoma and if it can assess marrow involvement reliably, it could offer a one-stop solution. Thus, whether FDG-PET can replace BMB has significant clinical implications. There are several factors that need to be considered while answering this question including the implications in each histological subtype of lymphoma, its therapeutic impact and whether or not it is a predictor of adverse outcome.

As per the new Lugano classification, BMB is not routinely required in Hodgkin's lymphoma if an FDG-PET is performed and in DLBCL, it is needed only when FDG PET/CT is negative for marrow involvement[7]. In HL, bone marrow involvement is uncommon in early disease. In advanced-stage disease, bone marrow involvement by BMB is not a major adverse prognostic factor[1]. FDG-PET has a better yield than BMB and has been proposed as a sensitive method for detecting bone marrow involvement though it may not be an independent predictor of the outcome[8]. In NHL, the necessity for a BMB is debatable. In early DLBCL, marrow involvement has low incidence and in presence of normal haematological parameters and non-bulky disease, BMB can be safely omitted and replaced by FDG-PET. In advanced disease, FDG-PET has good sensitivity for marrow involvement but can miss low volume marrow involvement and involvement by discordant histological type (small cells)[9]. When FDG-PET is negative, BMB is recommended. Two possible justifications for BMB in patients with a positive FDG-PET are that BMB can characterize histology of lymphoma infiltrates in the marrow which is of prognostic significance since concordant marrow involvement (*i.e*. by large cells) is a significant adverse factor. Second, even though it is established that BMB positive patients have worse outcome, same cannot be said about FDG-PET positive marrow, since a few available studies show that it is either prognostically insignificant or at least inferior to BMB[10,11]. In follicular lymphoma, marrow involvement is common and is a well-established adverse prognostic marker. Studies report FDG-PET to have low sensitivity in the range of 20-30 per cent whereas BMB is positive in up to 50 per cent patients[12,13]. Thus, FDG-PET cannot replace BMB in FL[8]. The criteria for categorizing FDG-PET positivity also need consideration. Focal marrow uptake more than liver is recommended as the criteria for

positivity[10]. Diffuse homogeneously increased marrow uptake may or may not signify marrow involvement. Studies in HL show that marrow with diffuse FDG uptake is mostly negative on BMB, but studies in NHL show lymphoma positive marrow involvement ranging from 22 to 100 per cent[8,14]. The available literature shows that diffusely increased FDG uptake in marrow is more likely to be positive on BMB in FL compared to HL, more so in patients with advanced disease[15].

Jitani *et al*[16] in this issue have evaluated the utility of FDG-PET in detecting bone marrow involvement in lymphoma in comparison to BMB. Sensitivity and negative predictive values for focal (±diffuse) FDG uptake in detecting marrow involvement were 100 per cent in both HL and NHL in comparison to BMB. Specificity and positive predictive value increased to 100 per cent in both when the resolution of FDG uptake in follow up was included as a criterion for involvement. The number of FDG-PET positives for involvement was more than BMB-positive cases in both HL and NHL. The authors have used at least one focus of FDG uptake with or without diffuse uptake as a marker of marrow involvement which is probably the most logical approach. In their study, the authors did not find any case of purely diffuse FDG uptake in NHL which turned out to be positive on BMB[16]. In the indolent lymphomas, included BMB had more positive outcomes for marrow involvement. In this prospective study, the authors have therefore rightly concluded that FDG-PET should be sufficient for staging HL and BMB may be avoided if a follow up FDG-PET is planned. In aggressive NHL (DLBCL) and indolent NHL (follicular lymphoma), if baseline and follow up FDG-PET is performed, and if there is presence of marrow involvement on PET, BMB may be precluded. However, if marrow FDG-uptake on PET/CT is absent, then a BMB should be done. They have suggested a higher SUVmax for involved marrow, but no defining cut-off values are available in literature[17]. We feel focal marrow uptake more than liver is a reasonable criteria for positivity.

The histological subtype of lymphoma is thus the most important factor influencing the choice of modality for staging the marrow. Further studies in FL and the other indolent lymphoma subtypes are needed to establish the utility of FDG-PET *vis-a-vis* BMB for marrow involvement. The strength of this study was its prospective nature, but long-term follow up and outcome analysis would be desirable to give a better idea as to whether the higher diagnostic accuracy of PET/CT translates into differences in outcome especially when the resolution of FDG uptake is taken as a criterion for involvement. Furthermore, the influence of FDG-PET on upstaging disease and subsequent treatment decisions would be useful to prove its utility. Large-scale, multicenteric prospective studies, preferably randomized controlled trials with a focus on outcome, in the Indian population are desirable to delineate the true diagnostic accuracy of FDG PET/CT in various lymphoma subtypes, to define the exact standardized criteria for marrow involvement on FDG PET/CT and most importantly, its impact on the outcome. Till then, BMB will continue to remain important at least in DLBCL patients who are negative for marrow involvement on PET/CT and in all cases of indolent lymphoma.

***Conflicts of Interest*:** None.

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