Review Article

Present role and future perspective of PET-CT in marginal zone lymphoma

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Abstract: The classification of the marginal zone lymphoma (MZL) among the 'non-FDG avid' lymphomas has discouraged the routine use of metabolic imaging in the evaluation of patients affected by this subtype of non-Hodgkin lymphoma. Nevertheless, recent data demonstrated that despite a significant heterogeneity due to different factors (location of the disease, morphological appearance and histological features of the main lesion) most of MZL lesions are detected by 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET), particularly in splenic and nodal MZL. The higher detection rate of the metabolic imaging with respect to the conventional radiological work-up may improve the accuracy of the MZL staging, mainly due to upstaging, in a significant number of patients, although the impact of this staging improvement on the management of the patients has not been measured yet. Preliminary promising results seem to indicate the potential usefulness of 18F-FDG PET as marker of treatment response, though its prognostic value remains uncertain. The role of the metabolic imaging in the clinical management of MZL is still an open question, needing more extensive studies including larger cohorts of patients, to be fully answered.

Keywords: Marginal zone lymphomas (MZLs); 18F-fluorodeoxyglucose positron emission tomography imaging (18F-FDG PET imaging); staging and response assessment

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Introduction

Marginal zone lymphoma (MZL) is the third most common subtype of non-Hodgkin lymphoma, representing 10% of all non-Hodgkin lymphoma cases in Western countries (1). The MZL includes three different entities: splenic MZL (SMZL), nodal MZL (NMZL) and extra nodal MZL of mucosa-associated lymphoid tissue (MALT) lymphoma with specific diagnostic criteria, clinical behavior and therapeutic implications (2-4).

Primary splenic and NMZLs are rare, each counting approximately less than 2% of lymphomas, whereas the extra nodal MZL of MALT type is more frequent, representing approximately 7–8% of the total number of non-Hodgkin lymphoma cases (1,5-7).

SMZL typically involves the spleen, hilar lymph nodes, bone marrow (BM) and, frequently, the blood. Some cases of disseminated MZL may present with splenomegaly and lymph node enlargement at distant sites. Approximately 20% of patients have simultaneous autoimmune manifestations (8-10).

NMZL usually presents with disseminated lymphadenopathy (mostly cervical and abdominal), with

or without BM and blood involvement at diagnosis. The disease is often advanced at presentation and 10–20% of patients have B symptoms. Initial staging follows the rules for other nodal indolent lymphomas, with the main goal to discriminate localized from advanced-stage disease and to have a measurable disease for evaluation of treatment response (11-13).

MALT lymphoma originates from B cells in the marginal zone of the MALT and can potentially affect any mucosal site usually in a context of chronic antigenic stimulation due either to infections or autoimmune disorders. Although the stomach is the most frequent localization, also lung, ocular adnexa and salivary glands may be sites of MALT lymphoma, while other localizations including liver, breast, bowel and thyroid are rare. Most often it remains localized within the tissue of origin, but spreading is not uncommon, and disseminated disease, including BM involvement, is reported in 25% to 50% of cases and seems more common in non-gastric cases (14-19). Because of the risk of occult disseminated disease, extensive work-up procedures are recommended in all MALT lymphomas, irrespective of their presentation site (5,6,20).

Standard diagnostic work-up of MZLs usually comprises BM aspirate (with morphology and flow cytometry), BM biopsy and complete chest and abdominal computed tomography (CT) scan. Magnetic resonance imaging is preferred to investigate orbits and salivary glands.

Esophagogastroduodenoscopy with multiple biopsies can be considered to exclude a concomitant gastric lesion while endoscopic ultrasound is effective to better define gastric wall infiltration and peri-gastric lymph node involvement, particularly when localized radiotherapy is planned (5,6,20). In SMZL abdominal sonography may give additional information for the detection of splenic focal lesions (11,12).

Discussion

PET-CT in MZL staging

The 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) imaging has generally been considered of little clinical utility in MZL. The Lugano Classification has not supported the use of 18F-FDG PET scanning for staging of MZL considering the low 18F-FDG avidity of these indolent lymphomas and the CT has been confirmed as the whole-body imaging of choice for routine staging and response assessment in this sub-type of lymphoma (21,22).

The classification of the MZL among the 'non-FDG avid' lymphomas is based on heterogeneous and contradictory results published by several studies that have reported values of the 18F-FDG PET detection rate (DR) in MALT lymphomas ranging from 22% to 100% (23,24).

Several pathological and clinical characteristics of the disease and lesions have been proposed to explain this wide range of PET sensitivity rates.

The location of the primary lesion significantly influenced 18F-FDG avidity of MALT lymphoma, with better 18F-FDG PET DR in bronchial (average DR: 95%) and head-and-neck (89%) lesions compared to those involving stomach (40%) and ocular annexa (50%).

Among morphological features, morphological gross appearance resulted as most important factor for PET results. Lesions presenting as protrusion, polyp or mass-forming lesions had higher 18F-FDG uptake than superficial, chronic gastritis-like and low thickening lesions. Also, tumor size, Ki-67 score and clinical stage have been demonstrated in some studies to be significantly correlated to 18F-FDG uptake in primary gastric and extra-gastric MALT lymphoma (25-31).

Another explanation of the different 18F-FDG PET DR for different lesion sites of MALT lymphoma may lie in the 18F-FDG tumor-to-background ratio. In fact, the lungs have almost no background uptake, whereas in other sites 18F-FDG uptake may be increased both physiologically (e.g., in the orbital region and gastrointestinal tract) and due to inflammation (such as in gastritis): this physiological or inflammatory uptake of 18F-FDG in some anatomic regions could mask the presence of a MALT lesion (32-35).

To increase the lesion/background contrast Mayerhoefer *et al.* (36) tested a delayed PET scan technique in a small series of patients. They showed that delayed scan imaging performs better than standard-time-point PET imaging: the patient-based sensitivity increased to 76.9% from 53.8% and the diagnostic accuracy improved both in gastric and extra gastric lesions.

Few studies investigated the DR of 18FDG PET in SMZL and NMZL. Albano *et al.* (37) evaluating retrospectively a cohort of 51 patients with SMZL reported pathological metabolic findings in 76% of cases, with a pattern mainly characterized by a diffuse splenic uptake. The 18F-FDG uptake was correlated with Ki-67 score but not with any histological, epidemiological and morphological features.

Vaxman *et al.* (38) in a mixed population of 110 MZL cases described a baseline FDG PET sensitivity of 82.7% in 29 patients with SMZL and 76.4% in 17 with NMZL,

respectively. The DR was higher than that of MALT lymphoma (62.5%; 64 patients).

Nevertheless, despite this wide variability, the overall 18F-FDG PET sensitivity appears quite high: the pooled estimate value of DR is 71% (95% CI: 61–80%) (23). According to these data the classification of MZL among the not FDG avid lymphomas could be now reconsidered also as a result of the improved performance of modern PET-CT.

The good sensitivity of 18F-FDG PET in the detection of MZL lesions is also confirmed by the higher accuracy of the metabolic imaging compared to the conventional radiological work-up in MALT lymphoma, showing a similar trend to that registered in aggressive NHL (25,27,29,38-42).

18F-FDG PET imaging detected more lesions in a significant number of cases determining an upstaging of the disease that ranged from 3% to 42% of patients in the different populations analyzed. No case of down staging was described in literature.

In most cases the upstaging was based on the detection of an increased number of nodal lesions but also on the recognition of distant lesions although the impact of this staging improvement on the management of the patients has not been clearly measured yet (42).

In keeping with these experiences, recent ESMO Guidelines have proposed to consider PET scanning in MALT lymphomas when localized treatment is planned. Metabolic imaging was also suggested in case of suspicious transformation to high-grade histology to target lymph node for biopsy and to stage cases where transformation has been demonstrated (5).

Although a BM involvement detected by 18F-FDG PET was described in several case reports the few data available nowadays do not suggest to replace the BM biopsy with the PET imaging (27,38). No study specifically explored the role of the 18F- FDG PET in the staging of SMZL and NMZL.

Prognostic value of PET-CT

The prognostic value of baseline 18F-FDG PET features, which has been validated in different subtypes of non-Hodgkin lymphoma, still remains uncertain in MZL.

In a large cohort of MALT lymphomas (n=173), Qi *et al.* (43) evaluated the relationship between 18F-FDG avidity of baseline PET and patient outcome [in terms of overall survival (OS) and progression free survival (PFS)] without significant correlations. Nevertheless, pre-treatment SUVmax was found to be an independent prognostic factor for OS but not for PFS. In fact, an increased SUVmax was associated only with a decreasing 5-year OS. Moreover, patients who presented lesions with SUV ≥10 had a higher rate of subsequent aggressive transformation (20% *vs.* 5%, P=0.035) and inferior OS (78% *vs.* 92%, P=0.008).

These results confirmed the data previously reported by Hwang *et al.* (44) in a mixed population with pathologically proven gastric lymphoma (34 MALT and 52 aggressive non-Hodgkin's lymphoma) showing that high SUVmax could predict poorer OS.

Conversely, a recent study (45) including 161 patients with 18F-FDG avid MALT lymphomas failed to demonstrated a significant prognostic value for any baseline 18F-FDG PET parameter, including different SUV values, metabolic tumor volume (MTV) and total lesion glycolysis (TLG). Also, Vaxman *et al.* (38) demonstrated that baseline PET results are not predictors of PFS and OS.

Mayerhoefer *et al.* (46) in a smaller population confirmed similar results, with the exception of baseline TLG that showed a significant correlation with 2-year PFS in both patients that received conventional treatment or immunotherapy regimen (based on rituximab and/or ofatumumab).

PET-CT in response assessment

The assessment of the response to treatment with the 18FDG PET in MZL was investigated in few studies including small number of patients (25,35,47-49). The results demonstrated that the metabolic response reflects with good accuracy the effectiveness of the therapy in patients with baseline FDG avid MALT lymphomas. More consistent data were collected at the end-of-treatment (EOT) in patients with primary gastric and lung disease but also the interim metabolic response during the treatment was tested (47,49). Both visual and semi quantitative approaches were applied in the response evaluation and the reduction of SUVmax value appears to provide an effective tool to discriminate responders from non-responders but no cut-off value could be determined. Only one experience has been published concerning the use of the Deauville criteria (21) for response assessment in MALT lymphomas (38). The Authors reported that patients achieving a complete metabolic response (defined by a Deauville score 1–3) after the end of treatment had better PFS than those with residual disease (Deauville score 4–5),

but this response classification was unable to discriminate subgroups with different OS.

The low number of patients enrolled, different therapeutic approaches used (radiotherapy, chemotherapy, immuno-chemotherapy and *H. pylori* eradication), different histologic characteristics of cases included, and, in particular, the different criteria applied for the evaluation of the metabolic response make premature to support an evidence-based role for PET/CT in monitoring the response to treatment in MALT lymphomas. Consequently, no consistent data about the prognostic role of the metabolic response are nowadays available. According to the only three studies dealing with this topic, it seems that a complete metabolic response to the therapy could predict a better PFS with a lower rate of disease relapse than that of patients with persistent metabolically active lesions after the end of treatment. No correlation with OS was demonstrated (27,38,49).

No study focused on the 18F-FDG response assessment has been published for the other MZL subtypes. However, in the recent ESMO Clinical Practice Guidelines for MZL (5) a negative EOT PET scan, if positive at diagnosis, has been included among the criteria to define a complete response to treatment in SMZL patients.

Conclusion and future perspectives

In conclusion, the present role of 18F-FDG PET in patients with MZL is not still well established. Despite a significant heterogeneity, MZL lymphomas appear 18F-FDG avid in most cases. Recent findings seem to indicate a potential clinical usefulness of 18F-FDG PET in the initial evaluation of these patients as also partially confirmed by recent clinical guidelines. Nevertheless, the few data available do not allows to support an evidence-based use of metabolic imaging in monitoring the response to treatment.

Promising preliminary results need to be confirmed and better characterized by more extensive studies including larger cohorts of patients.

To meet this need, the International Extranodal Lymphoma Study Group (IELSG) has recently launched the IELSG44 - PIMENTO trial ("FDG PET Evaluation for Marginal Zone Lymphoma and Its Prognostic Role: an International Multicenter Retrospective Analysis", NCT04333524) aimed at assessing the role of 18FDG-PET for the staging and for the assessment of response and outcome prediction in MZL.

The study is designed as a retrospective collection of patients with MZL enrolled in the prospective IELSG36 and IELSG38 trials and in the observational NF10 study, with the possibility to add additional cases from participating institutions.

Additionally, the ongoing IELSG47 MALIBU Trial ("Combination of Ibrutinib and Rituximab in Untreated Marginal Zone Lymphomas", NCT03697512) will provide perspective information about the role of 18FDG-PET for the evaluation of the immunotherapy in this subtype of lymphoma.

The future perspective of PET imaging in MZL may be built only by the growth of our knowledge in this field.

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Footnote

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