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Review Article

FDG-PET Scan: a new Paradigm for Follicular Lymphoma Management

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Abstract. In the present review, the reader will be led to the most relevant observations that prompted oncologists and haematologist to consider FDG-PET/CT as a new paradigm for FL management in clinical practice. The role of functional imaging in lymphoma staging, restaging, prognostication, and metabolic tumour volume computing will be reviewed in detail. Moreover, a special focus will be addressed to technical and practical aspects of PET scan reporting, which have been set during the last decade to ensure the reproducibility of the therapeutic results. Finally, the predictive role of PET/CT on long-term treatment outcome will be compared with another well-known prognosticator as minimal residual disease (MRD) detection by Immunoglobulin gene rearrangement assessment.

Keywords: Follicular Lymphoma; PET; Residual Disease; Prognosis.

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Introduction. Follicular Lymphoma (FL) in the second most common lymphoma subtype accounting for nearly one-quarter of all the non-Hodgkin lymphomas (NHL) in western countries.[1-2] Despite the remarkable progress in long-term disease control, nearly 20% of patients affected by this lymphoma entity ultimately experience treatment failure and disease progression within 2 years from diagnosis, with a 5-year overall survival (OS) of only 50%.[3] Attempts to identify these high-risk patients at diagnosis by the existing prognostic indexes such as the Follicular Lymphoma International Prognostic Index (FLIPI)[4] or FLIPI-2,[5] or conventional radiological assessment of treatment outcome have partially failed. Quite recently, a number of scientific reports focusing on the role of ^{18}F-Fluoro-deoxy-glucose positron emission tomography (FDG-PET) combined with computed tomography (CT) in FL staging, restaging and prognostication prompted clinicians and imaging experts to reconsider the use of FDG-PET/CT (PET) in this disorder. In lymphoma staging, PET provided information on the extra-nodal involvement of the tumour at disease onset as well as on the heterogeneity of clonal mechanisms underlying tumour spread and aggressiveness. New insights on early detection of tumour transformation to diffuse large B-cell lymphoma and practical guidelines on how to detect it have also been achieved thanks to a systematic use of PET in the for staging workup. The formal indication on PET use in FL came from the recently published Lugano recommendations for FDG-PET scan use for lymphoma staging and restaging, clearly stating that functional imaging with FDG-PET is the diagnostic standard tool for tumour burden assessment and treatment response

evaluation in several FDG-avid lymphomas, including FL.[6-7] PET scan performed at the end of therapy resulted in the only factor predictive of long-term disease control and overall survival in prospective multicentre clinical trials, and proved able to identify a fraction of patients (nearly 25%) with a particularly dismal prognosis. Quite recently, end-of-treatment PET scan has been compared to minimal residual disease detection by molecular biology in predicting long-term treatment outcome in FL. These studies showed that PET is able to image FL independently from the heterogeneity of the neoplastic clone, which could be missed by molecular biology technique. The latter, in fact, can precisely detect the single clonal disorder against which the molecular probe has been constructed but not the entire tumour burden when FL underwent a clonal evolution. The important information generated by PET results could in future allow clinicians to personalize treatment in FL maximizing the treatment efficacy and reducing the cost of maintenance treatment for patients whose disease could be controlled by standard immunochemotherapy treatment.

FDG-PET PET for FL Staging. FL is a lymphoma subset that proved FDG-avid in more than 95% of the cases.[8-10] Despite this high affinity, its use in FL for baseline staging in clinical practice became standard only in 2014.[6-7] Several head-to-head studies reported a higher sensitivity of FDG-PET/CT for FL staging compared to contrast-enhanced CT scan (Ce/CT).[6-7] In a cohort of 45 FL patients, CeCT ad PET/CT were performed in sequence for staging purpose: PET/CT detected more nodal (+51 %), and extranodal (+89 %) lesions than Ce/CT; five patients (11%) in early stage (I and II) by CeCT were upstaged to stage III or IV by PET/CT.[11] The overall accuracy of PET-CT and CeCT for tumour spread detection was 97% and 64%, respectively. The most frequently detected extra-nodal sites by PET/CT were bone marrow (13 Vs. 2) and spleen (11 Vs. 6). In a larger cohort of 142 FL patients prospectively enrolled in the Italian Foll-5 clinical trial, Luminari et al retrospectively reassessed the role of FDG-PET/CT and CeCT in the baseline staging.[12] FDG-PET allowed the identification of more nodal areas than CeCT in 32% of the patients and of 60 extranodal sites (ENS) in 47 patients. The most frequently discovered new ENS was bone/bone marrow (34), spleen (26), skin (12) and gastrointestinal tract (9). Interestingly, PET staging modified also the FLIPI score, and the latter increased in 18% of the patients and decreased in 6%. Finally, FDG-PET was able to upstage as much as 62% of the patients in early stage (I and II) by CeCT. As a matter of fact, bone marrow involvement (BMI) is the most frequently detected ENS in baseline FL staging.[11-13] Initial reports pointed towards a low sensitivity in detecting BMI by PET/CT: in the study by Le Dorz comparing CeCT Vs. FDG-PET/CT for initial staging in a cohort of 45 FL patients, PET detected 13 cases (29%) of BMI, 11 of them not detected by CeCT: 5 with a diffuse and 8 with a focal pattern of FDG uptake. Bone marrow trephine biopsy (BMB) was positive in all patients with diffuse uptake and in only 3 out of 8 with a focal uptake.[11] In another retrospective study on a cohort of 64 FL patients, Wohrer et al. again found that the most frequent ENS involved by lymphoma was the bone marrow, with a pattern of FDG uptake suggestive of BMI in 13 out of 24 (56%) with BMI by CeCT + BMB; nine had a diffuse uptake (all with a positive BMB) and four a focal FDG uptake (all with a negative BMB). However, in the remaining eleven patients with a positive BMB PET scan showed and "indeterminate" pattern of FDG uptake. Overall, the sensitivity of FDG-PET in detecting BMI was 54%.[13] In this pioneer study, however, some degree of diffuse FDG uptake could be observed in patients with a formally "negative" PET scan, prompting the Author's claim that a more sensitive threshold to detect an abnormal FDG uptake in BM could be able to pick-up all the cases with a BMB-proven BMI and a diffuse tracer uptake. This concept has been validated by a recently published study by Perry et al.[14] In a retrospective, single centre study of a series of 68 FL patients, evidence of BMI by FDG-PET/CT imaging was recorded in 16 patients (23.5%), 13 of them with a positive BMB. All the 8 patients with focal and 5/8 with a diffuse FDG uptake had a positive BMB. Three patients had a diffuse uptake, which disappeared with treatment and a positive BMB. On the other hand, a diffuse "unspecific" FDG uptake was observed in 17 patients (32.7%) with a negative BMB. As a consequence, BMI detected by the visual assessment of FDG-PET had a very high Negative Predictive Value (NPV): 100% and a disappointingly low Positive Predictive Value

(PPV) of 48.5%. By contrast, upon a quantitative assessment of PET resulting by Standardized uptake value (SUV) a SUV_{mean} value < than 1.7 or higher of 2.7 as able to distinguish patients with a non-invaded BM from those with a "true" BMI, showing a sensitivity and specificity of 100% in both cases. Out of 20 cases showing an "intermediate" SUV_{mean} value between 1.7 and 2.7 only 5 had a biopsy-proven BMI.[14] A particular interest of functional imaging in the baseline staging of FL is the early detection of transformation into a large B-cell lymphoma. This phenomenon, which occurs in 16% to 60% of the cases, depending on the length of follow-up and re-biopsy policy, is a clonal evolution from a classical FL, and it is characterized by an increased number of large B cell centroblasts.[15-16] The definition of FL transformation has in the past included progression from grade 1-2 to 3 or development of a diffuse pattern "d'emblée" with persistence of follicular morphology. The clinical behaviour of a transformed FL (tFL) is very aggressive, and treatment outcome is usually poor, with a median survival from the transformation of 1.2 years. A prompt identification of patients with tFL is therefore needed, as these patients could be treated from the beginning with intensive chemotherapy followed by autologous stem cell transplantation and, once in CR, could experience prolonged survival.[17] Several attempts have been made to correlate the histologic FL grade and FL transformation with the intensity of FDG uptake in PET/CT. In general non-tFL show a moderate FDG avidity, with a SUV_{max} values never exceeding 11.[18] On the other hand, the majority of tFLs have SUV_{max} values comparable to that of Diffuse Large B-cell Lymphoma (DLBCL).[19] In a series of 17 FL and 2 tFL staged at baseline, Kharam et al. were not able to show a significant differences in the entity of FDG uptake across the three histologic grade of FL; the mean SUV_{max} being 5.8 ± 2.6 for grade 1, 8.1 ± 4.8 for grade 2, 7.9 ± 1.3 for grade 3 (p= 0.1). By contrast, a significant difference was recorded between non-tFL and tFL: 7.66 ± 4.59 Vs. 13.9 ± 10.2 ($p<0.01$).[20] Quite recently, Novelli et al. in a longitudinal observational study performed on 16 FL and 5 DLBCL patients during 3.5 years, undergoing a PET-guided biopsy in the hottest FDG uptake site, were able to demonstrate a close correlation between histologic grade and the SUV_{max} detected on the biopsied node. The SUV_{max} was 6.7 (3.0-146) for grade 1, 9.3 for grade 2 (4.3-13-3), 12.7 (5.0-24.0) for grade 3a and 13.5 (3.0-40.0) for grade 3b and DLBCL. The Ki-67 (r=0.73) and FL grade (r=0.75) at the biopsy showed significant correlation with the SUV_{max} at diagnosis ($p<0.01$).[21] Wondergem et al. compared 18F-FDG and 3'-Deoxy-3'-18F-Fluorothymidine (FLT) PET scan to detect FL transformation. In this study, 18F-FDG and 18F-FLT PET scan were performed in 17 non-tFL and tFL, and the highest SUV_{max} was measured in both scans in every patient. SUV_{range} was also measured, defined as the difference between the SUV_{max} of the lymph node with the highest and lowest uptake per patient. The highest SUV_{max} was significantly higher in tFL than in non-tFL, both in FDG and FLT-PET ($p<0.001$). The SUV_{range} was significantly higher for tFL than FL with FDG-PET (p=0.029) but not with FLT-PET (p=0.075). The ability of FDG-PET to discriminate between FL and tFL was superior to that of FLT-PET for both the highest SUV_{max} (p= 0.039) and the SUV_{range} (p=0.012). The cutoff value of SUV_{max} to differentiate FL and tFL with FDG-PET with the highest sensitivity (100%) and specificity (82%) at a ROC analysis was 14.5.[22]

In conclusion, FDG PET proved more accurate compared to standard radiological means in FL staging, being able to upstage as much as 62% of the patients in early stage (I and II) by CeCT, with the highest sensitivity for ENS and, first among them, bone marrow. SUV_{max} values > 10 are usually found in grade 3 or transformed FL.

FDG-PET for FL Prognostication at Baseline. Quantitative metrics for PET scan assessment have been used to assess the prognostic role of baseline imaging with FDG-PET. In a retrospective study including 45 histologically proven FL patients treated with Rituximab and Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP), Le Dorz et al. showed a strong predictive value on treatment outcome of baseline FDG-PET score. The latter assigned 1 point for each of the following: (a) 1 point for osteo-medullar FDG uptake; (b) 1 point for $SUV_{max} \geq 15$, (c) 1 point for extra-nodal involvement other than BMI on PET; (d) 1 point for the largest diameter of lesion ≥ 7 cm., (e) 1 point for number of nodal sites involved by lymphoma of PET ≥ 6. Its ability to predict an incomplete response or an early relapse was compared with follicular lymphoma prognostic

index (FLIPI) using a Receiver Operation Curve (ROC) analysis for sensitivity, specificity and overall accuracy.[11] The ROC values for sensitivity of PET score ≥ 2 and FLIPI in predicting treatment failure were 0.856 (95% C.I. 0.745-0.967) and 0,594 (95% C.I. 0.387-0.801), with a significant advantage for PET score (p<0.0001). High tumour burden has been considered in the past an important prognostic factor in FL, and a number of parameters surrogate for high tumour burden have been proposed to identify poor-prognosis patients. Such are any nodal or extranodal tumour mass with a diameter larger than 7 cm., involvement of at least three nodal areas, each of which with a diameter ≥ 3 cm., systemic symptoms, substantial splenic enlargement, pleural effusion, orbital or epidural involvement and leukemic presentation.[23] More recently, more sophisticated tools such as functional imaging with FDG-PET/CT allowed displaying the morphology and the functional activity of tumour burden. Moving from quantitative metrics of FDG-avidity such as SUV_{max}, dedicated software permitted to quantify the metabolically active tumour volume (MTV).[24] The latter, calculated on baseline FDG-PET scan proved a very strong predictor of treatment outcome in Hodgkin Lymphoma,[25] in diffuse large B-cell lymphoma,[26] Primary Mediastinal B-cell lymphoma[27] and peripheral T-cell lymphoma.[28] In a pooled retrospective analysis on 185 FL patients enrolled in different prospective clinical trial and treated with immunochemotherapy, Meignan et al., upon visual assessment and manual contouring of all the lesions visible in baseline PET, using a fixed threshold method of 41% of the SUV_{max} value to measure MTV, demonstrated that MTV, computed at baseline FGD-PET scan and a cutoff value of 510 cm^3, was able to identify patients with a poor response to therapy, with a 5-Y PFS of 33% Vs. 65% for low and high MTV, respectively (p<.001) (**Figure 1).** In multivariate analysis only MTV and FLIPI-2 retained their independent prognostic value but, when both were used in a combined prognostic model, they were able to single out three classes with significant different 5-y PFS: (I) MTV ≤510 and FLIPI-2 0-2, median 5-Y PFS 69%; (II) MTV > 510 or FLIPI-2 3-5, 5-Y PFS 46% and (III) both MTV > 510 and FLIPI-2 3-5, 5-Y PFS 20%; group 1 Vs. 2: p=.007; Group 1 Vs. group 3: p<.001; group 2 Vs. group 3: p=.004.[29]

In conclusion, semi-quantitative parameters on baseline PET (Q-PET) such as SUV_{max} and MTV proved informative of long-term FL treatment outcome.

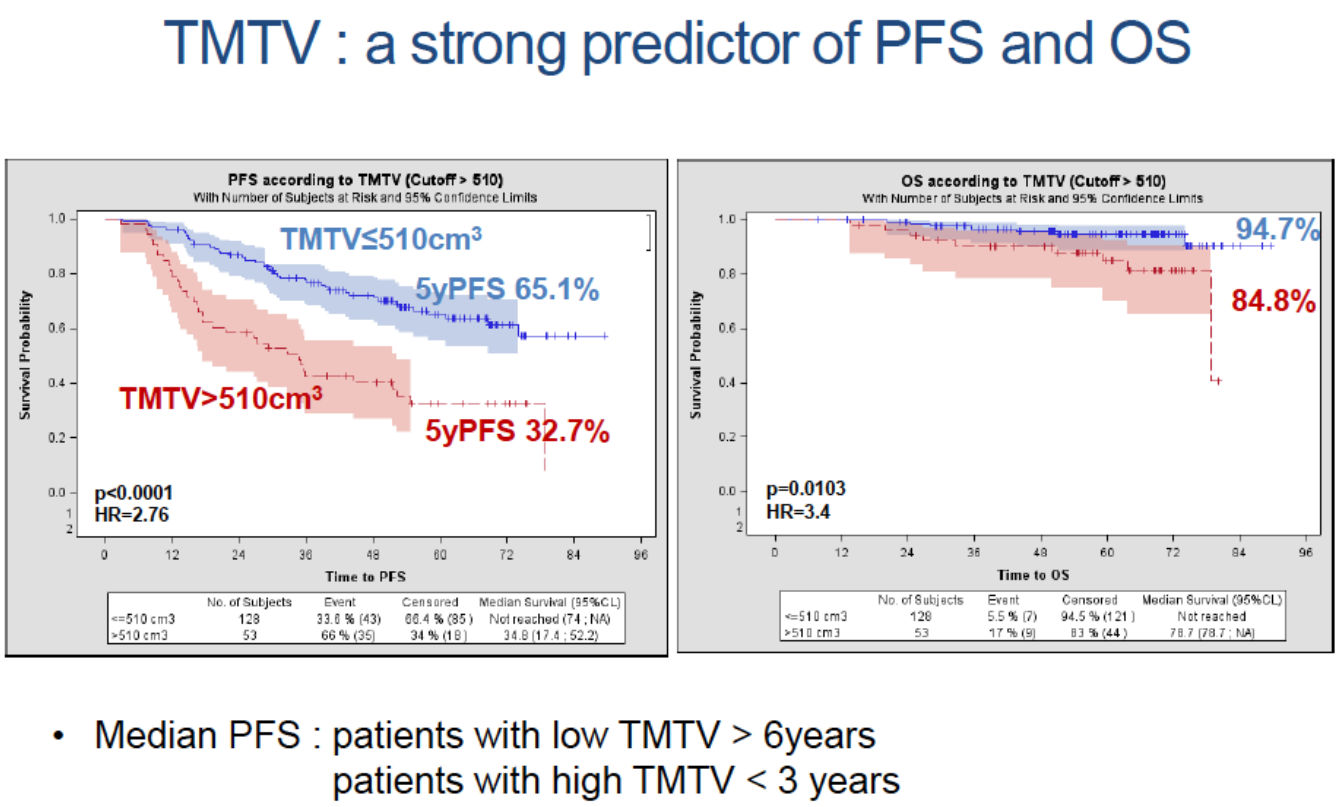

Figure 1. 5-Y PFS and OS according to baseline Total Metabolic Tumour Volume (TMTV). From Meignan et al.[29]

FDG-PET for Treatment Response Evaluation in FL. FDG-PET showed a higher performance in tumor restaging, compared to traditional radiological means in solid cancers,[30] HL and NHL.[31] In a retrospective study comparing FDG-PET/CT with contrast-enhanced CT scan in different NHL subtypes, PET showed higher sensitivity (86.1% Vs. 59.4%) and specificity (99.4% Vs. 96.1%) than CeCT alone.[32] Due to these and several other observations pointing toward its superiority in lymphoma restaging in different histotype, FDG-PET has been included among the mandatory investigation tests to assess treatment response in HL and NHL.[6] However, only three years earlier, after the publication of the results of three important trials, the LYSA trial PRIMA, the GOELAM trial and the FIL Foll-05 trial, aimed at assessing the efficacy of immunochemotherapy in FL, the interest of clinicians focused on the role of PET scan at the end-of-treatment for assessing the response.[33-35] Impressive similitudes in trial results have been reported across these studies, regarding: (a) the percentage of patients showing a positive end-of-treatment PET scan: 26%, 22%, and 24%, respectively; (b) treatment outcome of PET-positive Vs. PET-negative patients, with a 3-Y PFS of 33% Vs. 71%, a 2-Y PFS of 51% Vs. 87% and a 3-Y PFS of 35% and 66% respectively; (c) the prognostic role of end-of-therapy PET scan, which turned out as the only factor associated with overall survival in multivariate analysis in an independent way from other prognostic factors such as FLIPI. Interestingly, data were fully reproducible using a common readout for PET scan interpretation, the five-point Deauville scale (5P-S).[36] In a retrospective pooled analysis on 439 patients enrolled in the three trials whose PET scan images were centrally reviewed adopting 5P-S with a cut-off value of a positive scan ≥ 4, Trotman et al. confirmed the independent prognostic value of end-of-therapy PET scan. Patients with a score 4 or more had a 4-years PFS of 22.3% compared with 63.4% for patients showing a score 3 or less ($p<0.0001$).[37] It is also noteworthy that long-term survival was also significantly correlated with PET results, irrespective of second and further-line treatment: patients with a positive or negative PET after first-line treatment showed an OS of 87.1% and 97.2%, respectively ($p<0.00001$) (**Figure 2**).

In a recent, systematic review on the prognostic value of end-of-treatment FDG-PET in FL, Adams et al. reported the results of a pooled analysis of

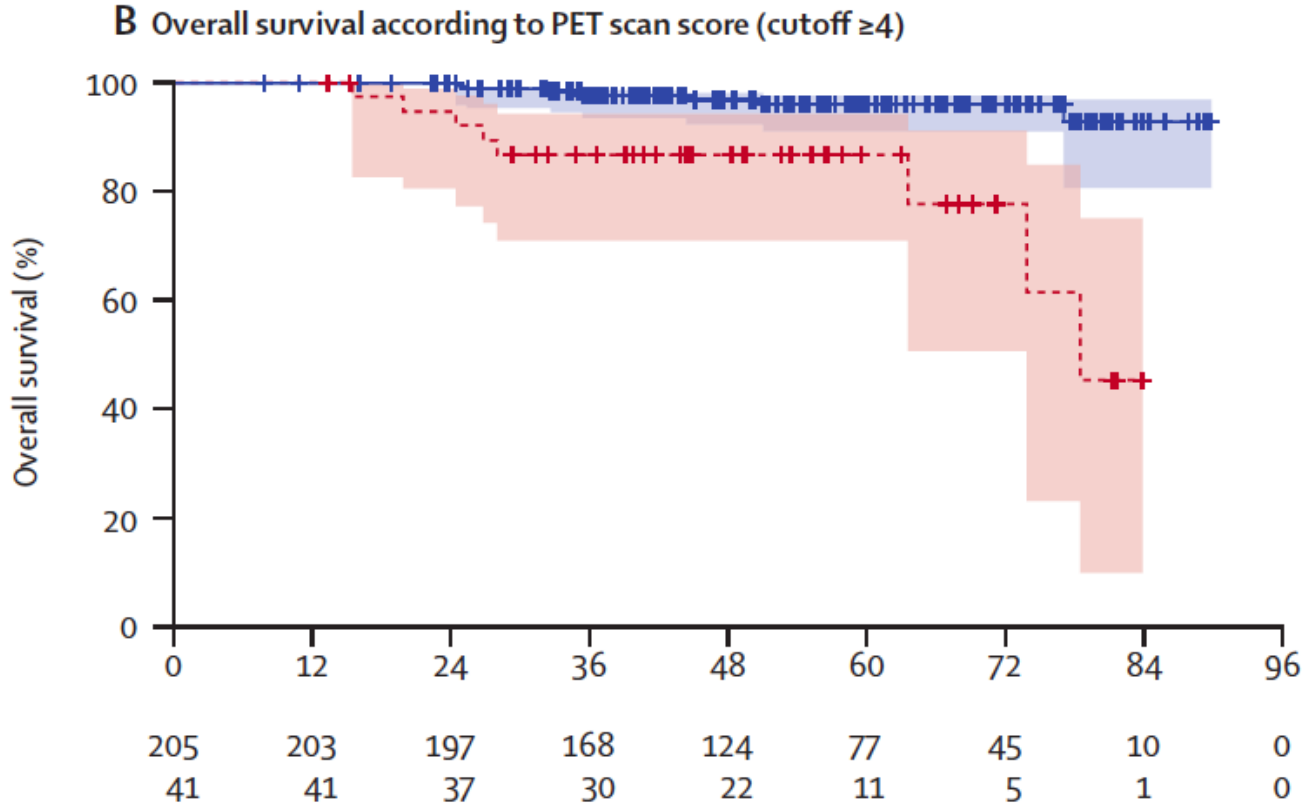

Figure 2. OS according to PET scan score. From Trotman et al.[37]

748 patients from eight different studies.[37] In six of them the association of a scan results with PFS was sought, and in five of them, a significant correlation between FDG positive patients and worse PFS was reported. Only three out four studies comparing OS and PET results showed a strict association, with a significantly lower survival in patients with a positive scan. Curiously in one single study[38] only a trend toward significance was found between 3-Y PFS and scan results, with a PFS of 74.4% and 38.2% for PET-negative and positive patients, respectively (p=0.083). In the same study FDG-PET was predictive of OS, showing mean OS of 95.2 and 45 months in PET-negative and positive patients, respectively (p<0.001). Overall, the above results seem to confirm the concept that relying on morphologic parameters alone such as tumour shrinkage after treatment is not adequate to predict long-term survival in FL. As a matter of fact, the association of radiological and functional imaging in the so-called IHP criteria for the first time showed that a tumour size reduction associated with a persistent FDG avidity had a much worst prognostic meaning than it would have been predicted by the classical radiologic IWC criteria alone.[39] Minimal residual disease (MRD), assessed on tumour DNA by molecular biology has been advocated as a predictive parameter on long-term treatment outcome in FL.[40] Upon systematic use of end-of-treatment PET scan to assess the response of first line treatment in FL, data on MRD and PET after therapy were concurrently available. In an interesting preliminary report, Luminari et al. tried to correlate the predictive role of both methods in the same patients enrolled in the Italian FIL study Foll-05.[41] FDG-PET scan was centrally reviewed and scored according to 5-PS,[36] and MRD was assessed on bone marrow aspirate with a qualitative and quantitative assessment of the BCL2/IGH fusion gene, after nested qualitative PCR.[42] A total of 41 subjects had available data on both PET and BCL2/IGH at the end of treatment. PET/MRD concordance was only 76% with a kappa value of 0.249, suggesting the both parameters were not strongly correlated. In univariate analysis, EOT PET was associated with poorer PFS (HR 3.61 p= 0.028) while MRD showed only a trend toward a shorter PFS (HR 2.54; P= 0.06).

In conclusion, there is largely documented evidence that achieving a complete metabolic response (CMR) at the end of treatment is the single most powerful predictor of long-term disease control and survival in FL.

FDG-PET for Radioimmunotherapy (RIT). In 2003 the Food and Drug Administration (FDA) approved the use of ^{131}I-tositumomab (Bexxar® Glaxo Smith Kline), and later of 90Y-Ibritumomab (Zevalin® Biogen-IDEC) and for the treatment of relapsed, refractory FL. Ibritumomab is the murine parent of the anti-CD20 antibody (IDEC) from which the human chimeric antibody rituximab was engineered. Both agents target the CD 20 antigen expressed on the surface of B-cell lymphoproliferative disorders. Upon binding of these MoAbs on their ligand on the cell surface, a cell apoptosis or a cell lysis does occur, mediated by the complement or by the Fc part of the antibody binding to the Fc receptor on the cytotoxic T-cells. A synergistic action of the radio-conjugate consists in the cytolytic action of the neoplastic cells by the β-particles emitted by the radiotracer.[43] The efficacy of both radio-conjugates in relapsed or refractory FL is similar, with an overall response rate of the 60%-83% .[44-46] Front-line treatment of high-risk FL with ^{131}I-tositumomab induce even higher overall response rate (95%), with as much as 75% of the patients attaining CR.[47] However, advantages of RIT over standard immunochemotherapy with R-CHOP in untreated FL were less evident in prospective, randomized studies and contradictory results have been published. In a well-designed prospective randomized trial, 532 patients with stage II-IV and grade 1-3 FL were randomly assigned to CHOP-R or CHOP-21 followed by 4-8 weeks after the 6th CHOP cycle by ^{131}I-tositumomab radioimmunotherapy. After a median follow-up of 4.9 years, the 2-year estimate of PFS and OS were 76% and 97% in the CHOP-R and 80% and 93% in the CHOP-RIT arm (p= 0.11 and 0.08, respectively).[48] These results were partially contradicted by another study with a longer patient follow-up. In a prospective, randomized international first line FL treatment aimed at assessing the role of ^{90}Y-Ibritumomab tiuxetan as consolidation treatment after chemo-immunotherapy, Morschhauser et al., after a follow-up spanning over 7 years, were able to demonstrate a significant advantage of the arm randomized to receive RIT consolidation compared to the arm addressed to no further

treatment (NFT). Patients receiving combination treatment had an 8-Y PFS of 48% compared to patients receiving NFT (22% $p < 0.001$). This difference remained significant in patients in CR/CRU (48% Vs. 32% p=0.008) and in PR (33% Vs. 10% p <0.001) after chemo-immunotherapy.[49] Importantly, in neither study, a significant and unexpected acute toxicity was reported. In long-term follow-up, only a non-significant, slight prevalence of secondary neoplasms and secondary myelodysplastic syndrome (MDS) was observed in the RIT arm compared to controls (26 Vs. 14, p=.086 and 7 Vs. 1, p=.042, respectively). ^{90}Y-Ibritumomab tiuxetan in combination with Carmustine, Cytarabine, Etoposide and Melphalan (so-called Z-BEAM conditioning regimen) followed by autologous stem cell transplant (ASCT) has been selectively used in transformed Follicular (TF) lymphoma. In a multicentre retrospective clinical trial evaluating ASCT after Z-BEAM conditioning regimen in 63 TF enrolled from 4 U.S. centres from 2003 till 2011, Mei et al. reported a very good long-term disease control, with a 2-Y PFS of 68% and an OS of 90%. The median time of ASCT from diagnosis of TF was 7.5 months, and the 2-Y non-relapse mortality was 0.[50] Due to a rather narrow therapeutic window, the therapeutic dose of both drugs should be calculated in vivo by injecting a tracer dose of a non-β emitting agent to predict the biodistribution of the drugs: the ^{131}I-labeled antibodies are γ-emitters and can be used for imaging and dosimetry. On the other hand, the ^{90}Y-labeled monoclonal abs like Zevalin® are beta-emitters and cannot be used for imaging, thus ^{111}In is used instead (in Europe) or ^{131}I-Ibritumomab (In United States). When ^{111}In-Ibritumomab tiuxetan is injected in the patient images of the tumour and the normal organs is produced. The therapeutic dose of ^{90}Y-Ibritumomab tiuxetan is determined by the patient's weight and baseline platelet count. Patients are first injected with Rituximab at the dose of 250 mg/m^2 to saturate CD-20 receptors on B-cell precursors and then with 5 mCi of ^{111}In labeled Ibritumomab on day 1 followed by tumour imaging in the next few days. Two or three whole-body images are required by the FDA to ensure normal biodistribution. On the day 8, the patient receives another dose of Rituximab, followed by ^{90}Y-Ibritumomab tiuxetan at the dose mentioned above. ^{131}I-Tositumomab can be used for imaging and treatment and has a more variable pharmacokinetic behaviour compared to ^{90}Y-Ibritumomab: the γ-photons emitted by ^{131}I (in addition to β particles) and the longer half-life of ^{131}I allow a more precise imaging definition and drug dosimetry in the single-patient basis. The dose injected varies with differences in body weight, tumour burden, and renal excretion of the radiotracer. The therapeutic dose is administered within 7 to 14 days from tracer dose and consists of 450 mg. of tositumomab saturating dose, followed by a 20-minute infusion of the patient specific ^{131}I-tositumomab dose. One day before tositumomab injection a saturating dose of potassium iodide is also needed to avoid concentration of the radiotracer in the thyroid. Thus, when a choice could be made between the two drugs (as in the United States) and bone marrow toxicity could be a concern, ^{131}I tositumomab tiuxetan should be preferred.[51] Tumour imaging pre-RIT could also be obtained with MoAbs conjugated with other radiotracers. Biodistribution radiation dosimetry and scouting of ^{90}Y-Ibritumomab tiuxetan have been made with ^{89}Zr-Ibritumomab.[52] The highest absorbed dose was observed in liver (3.2 ± 1.8 mGy/MBq), followed by spleen (2.9 ± 1.8 mGy/MBq), kidneys and lungs. The bone marrow dose was lower (0.52 ± 0.04 mGy/MBq). The correlation between predicted pre-therapy and therapy organ absorbed doses, based on ^{89}Zr-Ibritumomab tiuxetan images was very high (Pearson correlation coefficient r=0.97). However, technical problems limiting the use of RIT still exist. The first is the limited delivery into the tumour as the transport and uptake of the Monoclonal Antibodies (MoAbs) by the tumour is variable, and most of the injected dose still circulates in the plasma and targets normal tissues.[53] The second problem is the penetration in the tumour, which is variable and nonhomogeneous across the different tumour regions. The steps associated with tumour targeting by MoAbs are blood flow to the tumour extravasation across the capillary wall, diffusion en the extracellular fluid and binding to the tumour. Extravasation across the endothelium is the rate-limiting step; the estimated permeability of extravasation is 1 μm/s for FDG and 0.003 μm/s for MoAbs.[54] Finally, tumours are surrounded by a layer of extracellular matrix (ECM) proteins, such as collagen, elastin, fibronectin, which inhibit the penetration and dispersion of cancer therapeutic agents. ECM has been implicated in the treatment

resistance in solid tumours.[55] Thus, despite logistic and administrative problems for drug preparation and drug availability RIT with ^{90}Y-labeled monoclonal Zevalin® in Europe and ^{131}I-Tositumomab tiuxetan in U.S. remains an effective treatment for relapsed /refractory FL.

Conclusions. A large body of evidence suggests today that FDG-PET/CT is indeed a new paradigm for a modern FL management in clinical practice. It proved very accurate in FL staging, restaging, prognostication and RIT planning. Although informative on prognosis, MTV assessment at baseline still remains an investigational tool as standardization problems and unsettled thresholding still preclude its reproducibility in the daily clinical care.

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