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LETTER TO THE EDITOR

Debate on the value of end-of-treatment FDG-PET response evaluation in follicular lymphoma

Hugo J. A. Adams^a and Thomas C. Kwee^b

^aDepartment of Radiology and Nuclear Imaging, University Medical Center Utrecht, Utrecht, The Netherlands; ^bDepartment of Radiology, Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, Groningen, The Netherlands

Follicular lymphoma is the second most frequently diagnosed non-Hodgkin lymphoma subtype [1]. Whereas the 2007 Revised Response Criteria for Malignant Lymphoma [2] recommended computed tomography (CT) for response assessment in follicular lymphoma, the 2014 Lugano Classification [3] proposed ¹⁸F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) in all baseline FDG-avid lymphoma histologies, including follicular lymphoma. End-of-treatment FDG-PET is also supported by several other guidelines, such as the guidelines of the European Society of Medical Oncology (ESMO) [1] and National Comprehensive Cancer Network (NCCN) [4]. End-of-treatment FDG-PET imaging has two major roles in follicular lymphoma: (1) results may be used to inform a patient about his/her prognosis and (2) results may be used to guide further treatment.

Traditionally, prognostication in follicular lymphoma is usually performed using the Follicular Lymphoma International Prognostic Index (FLIPI), [5] or its successor the FLIPI-2 [6]. The original 2004 FLIPI score was based on a cohort of 1795 patients with the aim to predict overall survival (OS) and identified age ≥ 60 years, Ann Arbor stage III–IV, hemoglobin level < 120 g/L, serum LDH $>$ upper level of normal (ULN) and number of extranodal sites > 4 as most valuable risk factors. Patients classified as low risk (0–1 risk factors), intermediate risk (2 risk factors) or high risk (≥ 3 risk factors) had a 5-year OS of 90.6%, 77.6% and 52.5%, respectively (Table 1). The FLIPI-2 was predominantly developed to predict progression-free survival (PFS). In the FLIPI-2 cohort of 832 patients, the risk factors B-2 microglobulin $>$ ULN, longest diameter involved node > 6 cm, bone marrow

involvement, hemoglobin < 12 g/dL and age > 60 years were independently predictive for reduced PFS. Patients with low risk (0 risk factors), intermediate risk (1–2 risk factors) and high risk (≥ 3 risk factors) had a 5-year PFS of 79.5%, 51.2% and 18.8%, respectively. The FLIPI-2 was also predictive for OS, with 5-year estimates of 98%, 88% and 77% in the training cohort and 96%, 80% and 59% in the validation cohort, respectively (Table 1).

Recently, several studies have been published claiming end-of-treatment FDG-PET to have high value in predicting PFS in follicular lymphoma [7]. However, these results should be interpreted with caution. First, these studies suffered from inadequate methodology (the most notable concern is that patients with positive results were likely followed more closely, resulting in an earlier detection of relapse) [7]. Second, in follicular lymphoma, there is no clear definition for end of PFS. Therefore, several different criteria may be used: first clinical or radiological evidence of disease after attaining complete remission (only applicable in end-of-treatment FDG-PET-negative cases), increase in FDG avidity at follow-up PET scans, increase in tumor volume at follow-up CT, changes in laboratory assessments, development of symptoms, histological evidence of high-grade transformation, initiation of second-line therapies or death. Note that end of PFS as defined by several of the aforementioned criteria is not an indication to initiate second-line therapies or change patient management otherwise. Furthermore, it should be noted that increased FDG avidity on follow-up PET scans (which is not an infrequently used criterion) is insufficient proof to define end of PFS, since follow-up FDG-PET scans

Table 1. Value of the original FLIPI and FLIPI-2 and end-of-treatment FDG-PET in predicting OS in patients with follicular lymphoma.

Risk scores	Number of patients included	Low risk	Intermediate risk	High risk
Original FLIPI [5]	1795	5-year OS: 90.6%	5-year OS: 77.6%	5-year OS: 52.5%
FLIPI-2 (training cohort) [6]	832	5-year OS: 98%	5-year OS: 88%	5-year OS: 77%
FLIPI-2 (validation cohort) [6]	231	5-year OS: 96%	5-year OS: 80%	5-year OS: 59%
End-of-treatment FDG-PET result		Negative		Positive
Trotman et al. [15]	122	42-month OS: 96.5%		42-month OS: 78.5%
Dupuis et al. [14]	119	2-year OS: 100%		2-year OS: 88%
Lu et al. [21]	57	3-year OS: 96%		3-year OS: 60%
Trotman (pooled database) a [22]	439	4-year OS: 97.6%		4-year OS: 84.8%

^aThis study included patients from the studies by Dupuis et al. [14], Trotman et al. [15] and Luminari et al. [16].

have already been shown to suffer from a strikingly high false-positive rate as demonstrated in several lymphoma subtypes, with multiple studies reporting FDG avidity during follow-up to be caused by inflammation rather than progression of lymphoma [8–13]. Consequently, it should be emphasized that end of PFS as defined by many studies is not the most important outcome measure in follicular lymphoma and that the prognostic value of end-of-treatment FDG-PET should be defined by using other more meaningful outcome measures, such as the time interval between end-of-treatment response evaluation and initiation of a subsequent line of therapy (which should not be driven by FDG-PET results, because of the high risk of false positives, as mentioned previously), redevelopment of symptomatic disease or another robust prognostic outcome measure such as OS.

Unfortunately, there are currently no studies available evaluating the value of end-of-treatment FDG-PET in predicting time interval until subsequent treatment initiation or redevelopment of symptomatic disease [7]. On the other hand, some recent studies have evaluated the value of end-of-treatment FDG-PET in predicting OS (Table 1). The studies of Trotman et al., Dupuis et al. and Lu et al. included 122, 119 and 57 patients, respectively, and found end-of-treatment FDG-PET to be predictive of OS, with patients with a negative versus positive end-of-treatment FDG-PET result having a OS of 96.5% versus 78.5, 100 versus 88% and 96% versus 60%, respectively. Another study by Trotman et al. pooled cohorts of three prospective studies (Dupuis et al. [14], Trotman et al. [15] and Luminari et al. [16]) comprising a total of 439 patients and reported a 4-year OS of 97.6% for patients with negative and 84.4% for patients with positive end-of-treatment FDG-PET results. Note that these results are inferior to those of the (cheap and easily available) prognostic biomarkers as proposed by the original FLIPI [5] and FLIPI-2 [6] and that none of these studies corrected the predictive value of end-of-treatment FDG-PET for the FLIPI/FLIPI-2 [5,6]. Finally, after standard treatment, patients are usually not treated before the redevelopment of symptomatic disease, despite a high-risk profile of relapse. The generally good OS of end-of-treatment FDG-PET-positive patients also underlines that early treatment intensification (i.e., applying upfront additional therapy in patients with positive end-of-treatment FDG-PET results) can be considered unjustified, further nullifying the need for end-of-treatment FDG-PET. Also note that FDG-PET scans are expensive, provide patient discomfort,

expose patients to potentially harmful ionizing radiation, and are not available at all institutions.

There are several theoretical underpinnings that may explain the low value of end-of-treatment FDG-PET in predicting prognosis in follicular lymphoma. First, follicular lymphoma is generally considered incurable. Consequently, the absence of FDG-avid disease after treatment does not mean cure, but can only indicate that the majority of tumor bulk has responded and that the remainder tissue has become undetectable by FDG-PET due to its limited spatial resolution [17]. Second, studies in various lymphoma subtypes have shown that FDG-avidity after treatment initiation is caused by inflammation rather than viable lymphoma, resulting in erroneous prognostication [8]. Third, in follicular lymphoma, bone marrow involvement is detected by means of bone marrow biopsy in up to 50% of patients [18]. However, several studies have shown that FDG-PET is insufficiently able to detect bone marrow involvement in follicular lymphoma [18]. As a result, response to therapy of lymphomatous deposits lodging in the bone marrow cannot be assessed using FDG-PET. The same applies to the gastrointestinal tract, since studies have shown that FDG-avidity is absent in large proportions of patients with biopsy-proven intestinal involvement [19,20].

In conclusion, previous studies on the value of end-of-treatment FDG-PET in predicting PFS suffered from poor methodology, there is a lack of a uniform and clinically meaningful definition of end of PFS, and clear clinical benefits of predicting end of PFS are missing. Furthermore, clinical (cheap and easily available) prognostic indices such as FLIPI [5] or FLIPI-2 [6] have shown to have prognostic value surpassing that of end-of-treatment FDG-PET. Therefore, although several guidelines propose end-of-treatment FDG-PET for response evaluation in follicular lymphoma, there is no scientific base that supports its implementation in routine clinical practice.

Ethical approval

This article does not contain any studies with human participants or animals

Disclosure statement

No potential conflict of interest was reported by the authors.

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