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INTERIM 18 F-FDG PET IN LYMPHOMA: FROM PREDICTION OF RESPONSE TO RESPONSE-ADAPTED THERAPY. A NEW PARADIGM.

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18F-FDG PET have gained an unrivaled role in oncology. Developed and synthesized in 1976 at Brookhaven laboratories, and almost coinciding with the installation of the first PET scanner in 1974 at Washington university, it rapidly proved very useful in detection of different malignant tumours because of the high metabolic activity of most of them.

Lymphoma is one of the very first tumours that 18F-FDG PET proved helpful in its management. Nowadays its world widely accepted that 18F-FDG PET is highly valuable in staging, re-staging and before stem cell transplantation of Hodgkin lymphoma (HL) and high grade non-Hodgkin lymphoma (NHL)[1,2,3].

It wasn't much later that the potential value of 18F-FDG PET in evaluation of response to treatment has been recognized. A dramatic increase in the use of 18F-FDG PET for assessment of disease state after therapy have occurred in the last years[4], and whole issues in prestigious journals have been devoted to this subject (January 2008, PET clinics; May 2009 (Supplement), Journal of Nuclear medicine). It was soon recognized that standardization of the PET interpretation criteria is mandatory if reproducible data is to be expected. Several guidelines have been proposed[5], with the guidelines of the international harmonization project in lymphoma the most widely accepted and used one[6].

The idea of early evaluation of response to therapy using 18F-FDG PET after few cycles of chemotherapy developed later. It is based on a simple and logical theory: 18F-FDG PET can only detect tumour cells above a certain threshold, below which PET will return negative results in spite of the presence of viable tumour tissue (Figure 1). So a negative 18F-FDG PET study at end of therapy does not necessarily mean that the patient has no residual malignant cells, while if interim PET after one or two cycles of chemotherapy is negative, this means that the rate of cell kill is probably rapid enough to reach a complete eradication of malignant cells by end of treatment. The rational of interim PET is to define a prognostic index reflecting tumour chemosensitivity during first-line therapy, allowing early changes of therapy (escalation or de-escalation) adapted to specific situations[7].

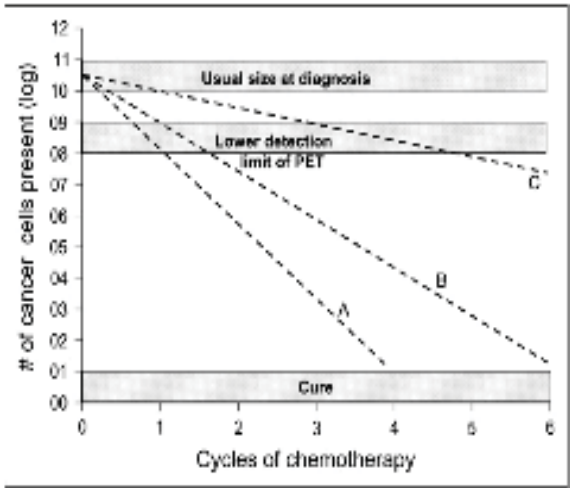

Figure 1: Lines A and B represent cell death rate which will lead to cure after 4 and 6 cycles of chemotherapy, respectively. Both will show a negative 18F-FDG PET on interim PET. Line C represents a slower rate of cell death. Its 18F-FDG PET at end of therapy will also be negative but its interim PET will show active residual disease. (Adapted from Wahl et al.)[5].

The idea gained rapid acceptance and it was proposed that interim 18F-FDG PET obtained during ABVD treatment provides the most important prognostic information for predicting treatment outcome in patients with HL[8]. Similarly, Dupuis et al. reported that the integration of PET in treatment evaluation of patients with diffuse large B cell lymphoma (DLBCL) offers a powerful tool to predict outcome[9]. These data encouraged the introduction of interim PET in the national comprehensive cancer network (NCCN) guidelines for management of HL and NHL[10] and in the European society of medical oncology (ESMO) clinical recommendations for diagnosis, treatment and follow up of HL[11]. However, this was not

without the appearance of more skeptical opinions refuting the prognostic value of interim PET[12,13].

On clinical ground, many factors seem to play a role in the outcome of interim PET. The time of interim PET is one of them. Would it make a difference if we do interim PET after 2 or 4 cycles? The answer lies within the cellular framework of different types of lymphoma. In HL, The Reed-Sternberg cells account for less than 1% of the tumour cell population. The rest of the tumour mass is surrounded by non-neoplastic mononuclear bystander cells. Thee cells are metabolically very active leading to intense 18F-FDG uptake. However, these cells are turned off very early in treatment (after one or two courses of chemotherapy). This characteristic architecture lead to a very high overall accuracy of information from interim PET performed very early during chemotherapy[14]. On the contrary, neoplastic cells constitute more than 90% of the cell population in DLBCL and the metabolic activity decreases continuously with cell killing. Thus interim PET after one or two cycles of chemotherapy provides an early evaluation of chemosensitivity, while after 4 cycles of therapy 18F-FDG uptake is more dependent on tumour regrowth[7].

Another factor that may play a major role in interim PET result is the time between the last cycle of chemotherapy and the 18F-FDG scan. In animal trials, tumour infiltration by inflammatory cells peaks 10 days after chemotherapy and is still above background on day 15[15]. This means that an interim PET study performed not more than 2 weeks from the last cycle of chemotherapy can lead to false positive results. The criteria of PET interpretation play a major role in the study outcome. Many studies have adopted the criteria of the international harmonization project in lymphoma[6]. It was soon recognized that these criteria, designed for evaluation of response to therapy at end of treatment, might not be very suitable for interim PET interpretation[16]. This inspired the experts to establish a new set of interpretation criteria in the first international workshop on interim PET in lymphoma in Deauville 2009 (Figure 2). The later depends on visual scoring of the degree of 18F-FDG uptake without consideration of the size of the lesion. In addition, Deauville criteria extended the minimal residual uptake (MRU) concept to involve lesions with uptake higher than the mediastinal blood pool activity but lower than the liver, increasing the specificity and lowering the false positive rate of the study.

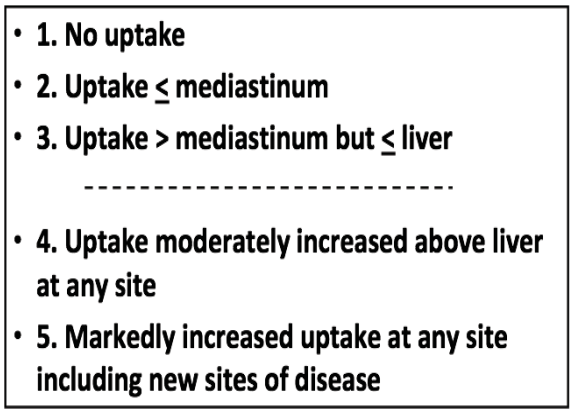

Figure 2: Deauville criteria. Five point scale for interpretation of interim PET. Adapted from Haioun et al. Presentation in the second international workshop on interim PET in lymphoma, 8-9 April 2010, Menton.

International validation studies for interim PET using the Deauville interpretation criteria have already published their first result in the second international workshop on interim PET in lymphoma[17]. At this study, 29% of patients with minimal residual uptake (MRU) and 64% of patients with positive result at interim PET show disease progression at a median of 7 months from diagnosis.

Many well-organized studies for use of interim PET in advanced stage HL (the RATHL study, the GITIL study), early HL (The RAPID study) and NHL (The MSKCC 01-142 study, the UK-NCRI study) are ongoing nowadays. With proper study design and suitable PET interpretation criteria, a more robust and reliable data is expected. This might lead to a more acceptance of the prognostic role of interim PET in lymphoma, and even incorporation of response-adapted therapy in the standard of care protocols. Meanwhile, it would be wise to use interim PET cautiously and only after standardization of PET study protocols and interpretation criteria (Table 1).

Table 1: Proposed indications of 18F-FDG PET for lymphoma in clinical practice.

	Baseline PET	Interim PET	End of treatment PET
HL	Clinical use	Clinical trials/ ? Clinical use with standardization	Clinical use
NHL	Clinical use	Clinical trials/ ? Clinical use with standardization	Clinical use

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