

Imaging in malignant lymphoma

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| ADC | apparent diffusion coefficient |
| CT | computed tomography |
| DWI | diffusion weighted imaging |
| FDG | fluorodeoxyglucose |
| FLT | fluorothymidine |
| HD | Hodgkin's disease |
| MIP | maximum intensity projection |
| MRI | magnetic resonance imaging |
| NHL | non-Hodgkin's lymphoma |
| PET | positron emission tomography |
| SUV | standardized uptake value |
| USPIO | ultrasmall superparamagnetic iron oxide particle |

The last decades have shown remarkable advances in radiology and nuclear medicine. With the continuous technological developments in imaging it is the role of both the radiologist and the nuclear medicine physician to provide adequate information concerning each modality and assist the clinicians in reconsideration of current guidelines in imaging. For example, 2-deoxy-2-[¹⁸F]fluoro-D-glucose ([¹⁸F]-FDG) positron emission tomography (PET) has become an important tool for diagnosis, staging, prognosis and evaluation of treatment response in oncology. This thesis addresses several aspects of imaging patients diagnosed with malignant lymphoma at initial presentation by studying the value of PET, PET integrated with computed tomography (PET-CT) and whole-body magnetic resonance imaging (MRI), including diffusion weighted imaging (DWI). In *Figure 1* these different modalities are illustrated.

Staging of patients with malignant lymphoma; value of PET and PET-CT

Until recently, CT was the single imaging modality for staging as well as therapy evaluation. However, particularly in therapy monitoring, its role during therapy evaluation is gradually being replaced by [¹⁸F]-FDG PET-CT. [¹⁸F]-FDG is a glucose analogue and is successfully used as a tracer in oncology, capitalizing on the enhanced glucose demand of most malignancies. An important advantage of [¹⁸F]-FDG PET vs. CT is the high-contrast resolution between malignant and normal tissues, the ability to detect disease at the subcentimeter level, and its ability to quantify glucose metabolism. This is usually done by means of semi-quantitative standardized uptake value (SUV), which may be of value as a biomarker for tumour grade.

In chapter 2 the introduction of PET and the added value of fused PET and CT images are illustrated in two patients with Hodgkin's disease (HD). In both patients the PET scan revealed increased [¹⁸F]-FDG uptake in regions where CT did not show any abnormalities. Fusion of PET and CT images visualized osseous localizations in both patients, which was confirmed by pathology in one patient. In both cases, the results of the PET-CT images altered the therapy based on the standard staging technique, the CT.

The detection of initial involvement of the spleen in patients with malignant lymphoma by CT is limited. The PET scan may have added value in detecting initial splenic involvement. In chapter 3 we determined the sensitivity and specificity of CT, PET, and PET-CT for initial detection of splenic involvement in patients with malignant lymphoma. In 111 patients the PET and CT scan, before and after treatment, were evaluated by two nuclear medicine physicians and two radiologists, respectively. True splenic involvement was defined retrospectively on the basis of the treatment response assessed with criteria revised in the International Harmonization Project on Lymphoma. For initial splenic staging, the sensitivity and specificity of CT, PET, and PET-CT were 91% and 96%, 75% and 99%, and 100% and 95%, respectively. In conclusion, with PET-CT sensitivity increased to 100% with retention of a high specificity of 95%.

Combined PET-CT is gradually replacing CT in therapy evaluation during and after treatment. In chapter 4 we tested the hypothesis that evaluation of the post-treatment PET scan is facilitated and improved by adding a baseline PET scan. First, 44 post-treatment PET scans of malignant lymphoma patients were evaluated by two experienced nuclear medicine physicians. Three weeks later the same post-treatment PET scans were presented together with the baseline PET scans (paired reading). The

scans were classified according to three categories: 1) no tumour; 2) unclear; 3) tumour. In 34% of malignant lymphoma patients addition of the baseline PET scan to the post-treatment PET scan affected the classification of metabolic response. False positivity was reduced by adding the baseline scan information, but there was no effect on false negativity. In addition, the amount of unclear classifications halved after paired reading. Observer agreement did not improve upon adding the baseline PET data. We concluded that if these results are confirmed for PET-CT systems, they favour the addition of baseline PET to the current work-up of patients with malignant lymphoma.

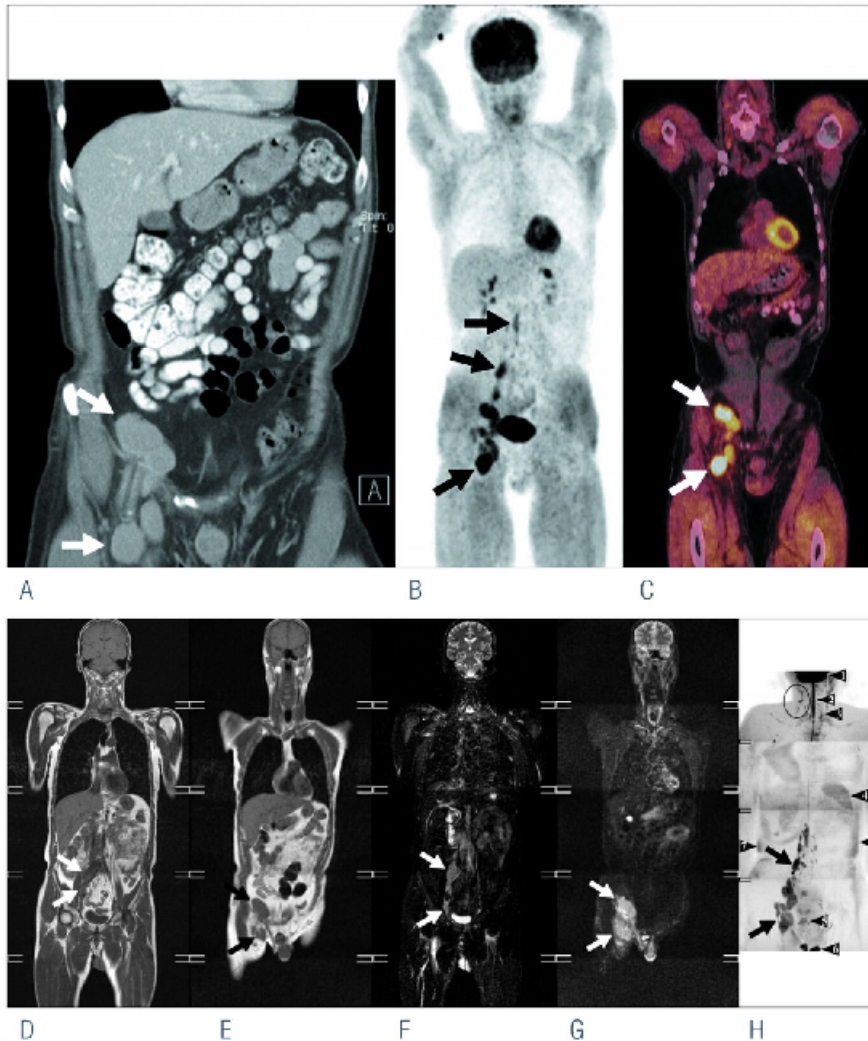


Figure 1. This figure illustrates the different modalities in staging of malignant lymphoma patients using the images of a 54-year-old man with a NHL (follicular B-cell lymphoma) and affected regions para-aortal, para-iliacal and inguinal resulting in stage II disease according to the Ann Arbor classification. This patient underwent a diagnostic CT scan, a [18F]-FDG PET-CT scan, and a whole-body (WB) MRI with a DWI scan. Evaluation of the modalities all resulted in stage II disease. Figure (A) is a coronal slice of the diagnostic CT scan illustrating enlarged lymph nodes at the right side of the pelvis and at the right inguinal region (arrows). The Maximum Intensity Projection (MIP) of the [18F]-FDG PET (B) displays all affected regions in one image (arrows). The coronal slice of the low-dose PET-CT scan (C) shows pathological [18F]-FDG uptake in the enlarged lymph nodes correlating to (A) (arrows).

The traditional way of using PET in oncological response evaluation is to measure fractional [18F]-FDG standard uptake value (SUV) change. However, baseline SUV may also carry prognostic information. In chapter 5, we tested the hypothesis that combining the two measures adds to relative change alone, in a meta-analysis. Since the PET evidence on lymphoma did not allow such meta-analysis we sought proof of principle in the literature on solid extracerebral tumours and neoadjuvant therapy. As expected, the relative change in [18F]-FDG uptake was the strongest indicator ($p < 0.0001$) for histopathologic tumour response. The baseline [18F]-FDG uptake was not significantly associated

as main factor. However, a significant interaction of baseline uptake and relative change after therapy was observed ($p < 0.001$). In conclusion, this meta-analysis provides support for the hypothesis of interaction of baseline [18F]-FDG uptake with its relative change during therapy in patients treated with neoadjuvant chemo(radio)therapy. These data corroborate and extend the need for standardization, quality assurance and control of PET studies quantifying [18F]-FDG in oncological treatment monitoring.

A disadvantage of CT and PET-CT, especially in the repetitive imaging of paediatric patients with malignant lymphoma, is the exposure to ionizing radiation. We describe the estimation of the risk of ionizing radiation focused on patients with malignant lymphoma in chapter 6. Simulations were performed using the Monte Carlo simulation tool and based on the current American imaging protocol for a child with HD and an adult with NHL (diffuse large B-cell lymphoma). Within the paediatric group with HD the average fraction of radiation-induced deaths was 0.4% for males and 0.7% for females; within the adults group with non-Hodgkin's lymphoma (NHL) these values were smaller: 0.07% for males and 0.09% for females, respectively.

Staging of patients with malignant lymphoma; value of MRI

The option of whole-body MRI scanning and the recent introduction of DWI created a novel alternative for (PET-)CT in imaging of malignant lymphoma. In a preliminary investigation, described in chapter 7, whole-body MRI, including DWI, was compared with CT for the initial staging of malignant lymphoma. Our first results were promising, as initial staging of malignant lymphoma using whole-body MRI (without DWI and with DWI) equals staging using CT in the majority of patients, and whole-body MRI never understaged relative to CT. Furthermore, whole-body MRI mostly correctly overstaged relative to CT, with a possible advantage of using DWI. Whole-body MRI may therefore be an attractive alternative indeed, and these preliminary results indicate future studies with larger sample sizes will be needed to determine the precise value.

In chapter 8 whole-body MRI, including DWI, was compared to the combination of integrated [18F]-FDG PET-CT and bone marrow biopsy in a pilot study for the initial staging of malignant lymphoma patients in 21 patients. In approximately 50% of patients staging using whole-body MRI, including DWI, is concordant with staging using the combination of [18F]-FDG PET-CT and bone marrow biopsy. Of note, bone marrow involvement was missed by both modalities in about 25% of cases. As DWI is able to provide functional tissue information (i.e. quantification of the diffusivity of water molecules by means of apparent diffusion coefficient (ADC) measurements), a second aim of this study was to assess the correlation between the ADC of DWI and the SUV of PET. There was a trend towards mild inverse correlation between the ADC_{min} and SUV_{max} . As this was the result of measurements in a small group of patients ($n=11$), future studies should assess their relative role with respect to reproducibility, tumour grading and assessment of response to therapy.

Future perspectives

In chapter 9 the results of the studies described in this thesis are interpreted and their potential implications are discussed. Future studies are proposed; e.g., a study to confirm the added value of a baseline PET to the interpretation of a post-treatment PET scan for PET-CT systems and a larger observer group with a more realistic clinical setting. The results of the meta-analysis corroborate and extend the need for standardization, quality assurance and control of PET studies quantifying [18F]-FDG in oncological treatment monitoring. More in general, other PET tracers (for example 3'-deoxy-3'-18F-fluorothymidine ([18F]-FLT) and other thymidine analogues) have been reported to be more specific for malignant tumors and to closely reflect tumour proliferation.

A disadvantage of repetitive PET-CT scans is the cumulative patient radiation dose and the associated mortality risk, which was confirmed in this thesis. With the introduction of whole-body MRI an alternative became available. The first results are promising and future studies with larger sample sizes have to confirm our findings and determine the place of whole-body MRI in the imaging guidelines for patients with malignant lymphoma. Moreover, MRI with ultrasmall superparamagnetic iron oxide particles (USPIOs) as MR contrast agents may help to improve detection of lymph node metastases.

With the introduction of PET-CT new therapeutic challenges originate, e.g., when PET-CT displays affected region(s) below the diaphragm and CT only displays superdiaphragmatic disease. Does the prognosis of this patient really differ from the prognosis of a patient with only disease above the diaphragm? A randomized study in patients with discrepant PET-CT and CT scans (one group therapy according to stage I/II and the other group therapy according to stage III) could answer this question. Another option is to treat these patients as stage I/II disease and observe whether their prognosis is worse compared to patients with concordant staging (stage I/II disease) of PET and CT.

This dilemma also arises in studies with MRI and PET-CT. Therefore, a concordant study with a large patient group is being performed. Discrepancies between the modalities should be resolved. Histopathology is the gold standard, yet not the most practical option in lymphoma patients. Follow-up is an important alternative, and not only a concordant study for staging but also for follow-up should be performed.

In conclusion, it can be stated that all modalities are of value in imaging malignant lymphoma patients. However, their precise role and place during staging, treatment, follow-up, and detection of possible recurrence needs to be established.

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Dr. H.M. E. Quarles van Ufford

Promotoren:

Prof.dr. W.P.Th.M. Mali, radioloog, UMC Utrecht

Prof.dr. O.S. Hoekstra, nucleair geneeskundige, VUmc Amsterdam

Copromotoren:

Dr. J.M.H. de Klerk, nucleair geneeskundige, Meander MC Amersfoort

Dr. R.A.J. Nievelstein, radioloog, UMC Utrecht

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