

The image features a minimalist design with a white background. A large, dark grey shape on the left side has a diagonal cutout at its top right corner. To the right of this shape is a vertical white gap, followed by another dark grey rectangular shape. The word "Chapter" is written in a bold, dark grey, sans-serif font, positioned on the left grey shape.

Chapter

Introduction and outline of the thesis

MALIGNANT LYMPHOMA

Epidemiology

Malignant lymphoma, a group of malignancies arising from lymphoid tissue, account for almost 5% of all cancers. With an incidence of 15/100.000 per year in Western countries, non-Hodgkin's lymphoma (NHL) is now the fifth most common malignancy after cancer of the breast, prostate, lung and colon. Although NHL incidence and mortality rates worldwide have risen sharply during the past few decades, the reasons for these increases are largely unknown.^{1;2} In the Netherlands, approximately 2500 patients with non-Hodgkin's lymphoma and 400 patients with Hodgkin's Lymphoma (HL) are diagnosed every year. (www.ikcnet.nl) The WHO classification of haematological malignancies stratifies malignant lymphoma primarily to their lineage, from B or T-cell/natural killer (NK)-cell origin, but classifies Hodgkin's lymphoma as a separate entity (WHO classification of neoplastic diseases of the hematopoietic and lymphoid tissue, in Sobin LH (ed)). Hodgkin's lymphoma is named after Mr. Thomas Hodgkin.

Thomas Hodgkin (1798-1866), pathologist, social scientist, and philanthropist, earned himself a place in the history of medicine with his original description in 1832 of the disease which bears his name, titled "On some morbid appearances of the absorbent glands and the spleen", in which he described six cases of enlarged lymph glands and spleen, with no infective origin. This paper did not attract much attention at the time. It was not until 1865 that Sir Samuel Wilks drew attention to Hodgkin's original observation, and labelled the condition "Hodgkin's disease". Less well known about Thomas Hodgkin are his wide humanitarian interests. Although he continued to write papers on medical subjects, the time he spent on medical practise dwindled as he became increasingly involved in matters of ethnological, philosophical and philanthropic nature. This related to his strong Quaker belief and his concern for the underprivileged.³

Clinical evaluation

After the introduction in the early 80's of the last century, CT scans were considered sufficiently reliable for staging and restaging of malignant lymphoma, and formed the basis of the International Working Group classification for lymphomas, a widely used method for evaluating disease and response to treatment.⁴ These standard modalities

include radiography of the chest and CT of the neck, chest, abdomen and pelvis with oral and intravenous contrast. So CT scanning has been the gold standard for the staging of lymphomas, but offers only structural information. CT provides relatively high sensitivity and specificity in pre-treatment staging, but has low specificity in assessment of response to therapy.⁵ For example patients with bulky disease prior to therapy often exhibit a residual mass post-treatment. CT scans determine the size and location of masses, but are unable to distinguish viable tumour from necrotic or scar tissue. From several studies it has become clear that the presence of residual lymphadenopathy is not predictive for relapse.^{6,7}

For the staging of malignant lymphomas, the Ann Arbor classification has been constructed, differentiating stages I-IV.⁸ For many years extended subtotal node irradiation (STNI) has been the treatment of choice for Hodgkin's lymphoma patients with stages I-II and lymphadenopathy above the diaphragm, with cure rates of up to 70-80%.^{9,10} However, a substantial amount of patients developed a relapse outside the radiation field, indicating that there must have been occult disease not properly detected by CT scan. Unfortunately, those patients being cured from Hodgkin's lymphoma, are at increased risk of developing second cancers.¹¹⁻¹³ We retrospectively evaluated all our Hodgkin's patients being treated at the VU University Medical Center with extended field irradiation from 1975 until 1995, for the relapse-free survival and the incidence of second cancers. The results of this study are described in *Chapter 2*.

The International Prognostic Index (IPI)^{14,15} and the International Prognostic Score (IPS)¹⁶ are currently used clinical prognostic indices for aggressive lymphoma and Hodgkin's lymphoma, respectively. However, either model uses static pre-treatment characteristics to predict the likelihood of response and survival of a given patient.

Functional imaging relies on the dynamic properties of the tumour mass both during and after treatment, to predict outcome. This thesis describes both functional imaging with ⁶⁷Galliumscintigraphy and Positron Emission Tomography using ¹⁸FDG for monitoring response during and after therapy.

⁶⁷Gallium scintigraphy is a metabolic imaging technique that relies on the accumulation of the isotope into viable lymphoma cells mainly via binding to transferrin receptors.^{17,18} ⁶⁷Ga is useful in assessing response in lymphoma, improving the specificity of CT. It has been widely used for the evaluation of malignant lymphomas.¹⁹⁻²³ However, The accuracy was limited due to the poor spatial resolution of gamma cameras, and high background uptake in liver, spleen, bone and bowel. The time involved in performing the scans (2-4 days post

^{67}Ga injection) and lack of a uniform approach to imaging with ^{67}Ga and appropriately high doses of radioactivity further limited its use.

FDG POSITRON EMISSION TOMOGRAPHY (PET)

Basic principles

PET allows for non-invasive imaging and quantification of physiological, biochemical and pharmacokinetic processes in vivo. Initially, PET was used as a research tool for investigating biologically active compounds, metabolic substrates, receptor ligands and drugs. In the early 90's, clinical applications in neurology, cardiology and oncology emerged.^{24;25}

PET as metabolic imaging technique uses radiopharmaceuticals produced by labelling metabolic markers as glucose with the positron-emitting radionuclide fluorine-18, which forms ^{18}F -2-fluoro-2-deoxy-glucose (^{18}FDG), which at present is the most widely used radiopharmaceutical in PET. Malignant cells are characterized by an increased glucose metabolism. ^{18}FDG preferentially accumulates within cells with a high rate of glycolysis and an increased cellular uptake of glucose, due to an increased expression of glucose transport proteins.^{26;27} When FDG is transported into the cell, it is phosphorylated by hexokinase to FDG-6- PO_4 . In contrast to phosphorylated natural glucose, FDG-6- PO_4 is not metabolised further. Therefore, it is essentially trapped in the cells. Rapid clearance from the circulation allows clinical imaging within about 60 minutes after injection and to complete a whole body evaluation within 1.5 hrs after tracer injection.

FDG is typically imaged by coincidence detection of two 511 KeV photons that are emitted in nearly opposite directions, by annihilation of the emitted positron after " bumping " into an electron. Dedicated or state-of-the-art PET cameras make use of Bismuth Germanium Oxide (BGO) multiple block detectors, which form a ring that surrounds the patient.²⁸ By scanning several axial fields (ranges between 15 and 25 cm), a whole-body image of the patient can be reconstructed.

Using this metabolic imaging technique, scar tissue or fibrosis can be distinguished from active lymphoma, which is of particular importance in post-therapy evaluation.

Methodological aspects

Many studies have been published on response monitoring with FDG PET in lymphoma and they report superiority over conventional methods.²⁹⁻³⁴ In the post-therapy setting, the results can be expressed in a two-by-two table. The PET is either positive or negative and the disease is present (relapse will be assessed in follow-up) or absent (no symptoms of active

disease will occur). A series of statistics are based on these combinations. Sensitivity, the number of true test positives divided by all cases with disease, and specificity, the number of true test negatives divided by all cases without disease, are the most common measures of accuracy. The methodological assessment and meta-analysis of the literature on FDG PET in post-treatment evaluation of malignant lymphoma until 2004 are described in *Chapter 3*.

In general, PET has a consistently high negative predictive value (NPV) in patients with HL and aggressive NHL. The false-negative rate with PET is mostly related to its inability to detect microscopic disease resulting in future relapse. The positive predictive value (PPV) of PET is generally lower and considerably more variable with generally lower average values in patients with HL compared with NHL.^{29;35} Still, the PPV of PET is substantially higher than CT, which has a reported PPV in patients with aggressive NHL of about 40-50% and in HL of only about 20%.^{36;37}

Even though the literature typically reports PET results in dichotomy, clinical practise may be different, and reports may contain probability estimates, and perhaps quite rightly so. The result of a FDG PET scan is usually expressed qualitatively, e.g. in terms of normal, faint, moderate and intense FDG uptake.^{38;39} Translated into a diagnosis, these qualifications should be interpreted somewhere between definitively benign, probably benign, equivocal, probably malignant and definitively malignant. Obviously, the dichotomy is lost. Likewise, each individual (non-invasive) test adds some probability measure and usually only invasively obtained tissue provides histological proof of disease.⁴⁰ Inherently, the visual assessment of FDG PET is subjective. For experienced nuclear medicine physicians, the interpretation of PET scans is based on the recognition of specific patterns and experience. While the PET scanner capacity has increased dramatically and most hospitals in the Netherlands now have access to fixed or mobile PET scanners, many nuclear medicine physicians were confronted with this new technique without having had much experience with it during their training. In *Chapter 4*, we measured the observer's variation among nuclear medicine physicians, also as a function of their PET experience.

Clinical imaging and prognosis

The International Prognostic Index (IPI), involving five static indices as prognostic markers, is currently used for aggressive NHL to predict the likelihood of response and survival of a given patient.¹⁴ PET on the other hand, relies on the dynamic properties of the tumour mass both during and after treatment to predict outcome. PET for therapy monitoring is performed after 2-3 cycles of chemo- or chemo-immunotherapy, to provide an early assessment to response. It is hypothesised that in chemosensitive disease, i.e., in patients with normalised midtreatment

scan, standard treatment may be sufficient, while in chemo-resistant disease, i.e., in patients with a positive midtreatment scan, standard treatment could be intensified. The comparison of FDG PET versus Gallium scintigraphy as a prognostic test during chemotherapy for NHL is described in *Chapter 5*.

The concept of chemo-sensitivity, as assessed by interim FDG-PET, may be useful to identify different patient risk groups. In a multicenter prospective cohort study (PALET study) the value of midtreatment FDG-PET was studied in patients with aggressive NHL, treated with (Rituximab)-CHOP chemo-immunotherapy. The study acronym PALET is short for Prognosis of Aggressive Lymphoma using Emission Tomography. The results of this study are described in *Chapter 6*.

Clinical risk scores are also used to identify risk groups for relapsed patients, as is the secondary age-adjusted IPI (sAA-IPI).⁴¹ We assumed that the combination of clinical risk scores and PET could help to refine the assessment of the individual prognosis. For this purpose, a prognostic model has been developed that combines clinical risk score and PET by analysing response parameters in a large cohort of patients with relapsed aggressive lymphoma. The results of this study are described in *Chapter 7*.

Guidelines

The widely used International Working Group criteria for response assessment of lymphoma, published in 1999, are based predominantly on CT and do not include PET as part of response assessment.⁴ Considering the more recent widespread use of PET in response assessment of lymphoma, it became clear that the International Working Group criteria warranted revision. For this purpose, the Competence Network Malignant Lymphoma convened an International Harmonization Project with five subcommittees among which the Imaging subcommittee. The aim was to develop guidelines for performing and interpreting FDG-PET for treatment assessment in lymphoma, to ensure the reliability of the method, both in the context of clinical trials and in clinical practise. The Imaging subcommittee, made up of nuclear medicine physicians, radiologists, and haematologists/oncologists, were selected for their expertise in PET and lymphoma. These guidelines are described in *Chapter 8*

REFERENCE LIST

1. Holford TR, Zheng T, Mayne ST, McKay LA. Time trends of non-Hodgkin's lymphoma: are they real? What do they mean? *Cancer Res.* 1992;52:5443s-5446s.

2. Coleman MP, Esteve J, Damiecki P, Arslan A, Renard H. Trends in cancer incidence and mortality. *IARC Sci.Publ.* 1993;121:1-806.
3. Sakula A. Dr Thomas Hodgkin and Sir Moses Montefiore Bart—the friendship of two remarkable men. *J.R.Soc.Med.* 1979;72:382-387.
4. Cheson BD, Horning SJ, Coiffier B et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J.Clin.Oncol.* 1999;17:1244.
5. Surbone A, Longo DL, DeVita VT, Jr. et al. Residual abdominal masses in aggressive non-Hodgkin's lymphoma after combination chemotherapy: significance and management. *J Clin.Oncol.* 1988;6:1832-1837.
6. Fuks JZ, Aisner J, Wiernik PH. Restaging laparotomy in the management of the non-Hodgkin lymphomas. *Med.Pediatr.Oncol.* 1982;10:429-438.
7. Canellos GP. Residual mass in lymphoma may not be residual disease. *J.Clin.Oncol.* 1988;6:931-933.
8. Smithers DW. Summary of papers delivered at the Conference on Staging in Hodgkin's Disease (Ann Arbor). *Cancer Res.* 1971;31:1869-1870.
9. Ferme C, Eghbali H, Meerwaldt JH et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N.Engl.J.Med.* 2007;357:1916-1927.
10. Noordijk EM, Carde P, Dupouy N et al. Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. *J.Clin.Oncol.* 2006;24:3128-3135.
11. Dores GM, Metayer C, Curtis RE et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. *J.Clin.Oncol.* 2002;20:3484-3494.
12. van Leeuwen FE, Klokmann WJ, Veer MB et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. *J.Clin.Oncol.* 2000;18:487-497.
13. Travis LB, Hill D, Dores GM et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J.Natl.Cancer Inst.* 2005;97:1428-1437.
14. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N.Engl.J Med.* 1993;329:987-994.
15. Shipp MA. Prognostic factors in aggressive non-Hodgkin's lymphoma: who has "high- risk" disease? *Blood* 1994;83:1165-1173.
16. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N.Engl.J.Med.* 1998;339:1506-1514.
17. Kaplan WD, Jochelson MS, Herman TS et al. Gallium-67 imaging: a predictor of residual tumor viability and clinical outcome in patients with diffuse large-cell lymphoma. *J.Clin.Oncol.* 1990;8:1966-1970.
18. Front D, Bar-Shalom R, Israel O. The continuing clinical role of gallium 67 scintigraphy in the age of receptor imaging. *Semin.Nucl.Med.* 1997;27:68-74.
19. Tumeik SS, Rosenthal DS, Kaplan WD, English RJ, Holman BL. Lymphoma: evaluation with Ga-67 SPECT. *Radiology* 1987;164:111-114.
20. Janicek M, Kaplan W, Neuberger D et al. Early restaging gallium scans predict outcome in poor-prognosis patients with aggressive non-Hodgkin's lymphoma treated with high-dose CHOP chemotherapy. *J.Clin.Oncol.* 1997;15:1631-1637.
21. Front D, Israel O. The role of Ga-67 scintigraphy in evaluating the results of therapy of lymphoma patients. *Semin.Nucl.Med.* 1995;25:60-71.
22. Israel O, Front D, Epelbaum R et al. Residual mass and negative gallium scintigraphy in treated lymphoma. *J.Nucl.Med.* 1990;31:365-368.

23. Even-Sapir E, Bar-Shalom R, Israel O et al. Single-photon emission computed tomography quantitation of gallium citrate uptake for the differentiation of lymphoma from benign hilar uptake. *J.Clin.Oncol.* 1995;13:942-946.
24. Brownell GL, Kairento AL, Swartz M, Elmaleh DR. Positron emission tomography in oncology—the Massachusetts General Hospital experience. *Semin.Nucl.Med.* 1985;15:201-209.
25. Maisey MN, Bingham JB. Modern imaging methods in oncology. *Acta Oncol.* 1992;31:889-902.
26. Warburg O. On the origin of cancer cells. *Science* 1956;123:309-314.
27. Yamamoto T, Seino Y, Fukumoto H et al. Over-expression of facilitative glucose transporter genes in human cancer. *Biochem.Biophys.Res.Comm.* 1990;170:223-230.
28. Visvikis D, Ell PJ. Impact of technology on the utilisation of positron emission tomography in lymphoma: current and future perspectives. *Eur.J.Nucl.Med.Mol.Imaging* 2003;30 Suppl 1:S106-S116.
29. Juweid ME, Wiseman GA, Vose JM et al. Response assessment of aggressive non-Hodgkin's lymphoma by integrated International Workshop Criteria and fluorine-18-fluorodeoxyglucose positron emission tomography. *J.Clin.Oncol.* 2005;23:4652-4661.
30. Spaepen K, Stroobants S, Dupont P et al. Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([¹⁸F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: is [¹⁸F]FDG-PET a valid alternative to conventional diagnostic methods? *J.Clin.Oncol.* 2001;19:414-419.
31. Spaepen K, Stroobants S, Dupont P et al. Can positron emission tomography with [(18)F]-fluorodeoxyglucose after first-line treatment distinguish Hodgkin's disease patients who need additional therapy from others in whom additional therapy would mean avoidable toxicity? *Br.J Haematol.* 2001;115:272-278.
32. Weihrauch MR, Re D, Scheidhauer K et al. Thoracic positron emission tomography using 18F-fluorodeoxyglucose for the evaluation of residual mediastinal Hodgkin disease. *Blood* 2001;98:2930-2934.
33. Naumann R, Vaic A, Beuthien-Baumann B et al. Prognostic value of positron emission tomography in the evaluation of post-treatment residual mass in patients with Hodgkin's disease and non-Hodgkin's lymphoma. *Br.J Haematol.* 2001;115:793-800.
34. Jerusalem G, Beguin Y, Fassotte MF et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. *Blood* 1999;94:429-433.
35. Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. *Blood* 2007;110:3507-3516.
36. Front D, Ben Haim S, Israel O et al. Lymphoma: predictive value of Ga-67 scintigraphy after treatment. *Radiology* 1992;182:359-363.
37. Vose JM, Bierman PJ, Anderson JR et al. Single-photon emission computed tomography gallium imaging versus computed tomography: predictive value in patients undergoing high-dose chemotherapy and autologous stem-cell transplantation for non-Hodgkin's lymphoma. *J.Clin. Oncol.* 1996;14:2473-2479.
38. Castellucci P, Nanni C, Farsad M et al. Potential pitfalls of 18F-FDG PET in a large series of patients treated for malignant lymphoma: prevalence and scan interpretation. *Nucl.Med. Commun.* 2005;26:689-694.
39. Castellucci P, Zinzani P, Pourdehnad M et al. 18F-FDG PET in malignant lymphoma: significance of positive findings. *Eur.J.Nucl.Med.Mol.Imaging* 2005;32:749-756.
40. Robinson PJ. Radiology's Achilles' heel: error and variation in the interpretation of the Rontgen image. *Br.J.Radiol.* 1997;70:1085-1098.
41. Hamlin PA, Zelenetz AD, Kewalramani T et al. Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. *Blood* 2003;102:1989-1996.