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Special reference to histological subtypes and epidemiology

Tiina Juntikka

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To my family – Juha, Edwin and Magnus

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ABSTRACT

Malignant lymphomas are currently classified as “mature B-cell neoplasms” and “mature T- and NK-cell neoplasms” (previously known as non-Hodgkin lymphomas) and Hodgkin lymphomas with over 60 subsequent subtypes. Specific diagnosis is crucial for treatment selection but many challenges prevail, including constantly evolving classification, biological complexity, and heterogeneity of lymphomas, not to mention the technical challenges.

Somatostatin receptors (SSTRs) can be used as molecular targets in imaging SSTR-expressing tumors and in their treatment. It is known that lymphomas express SSTRs variably, but their clinical significance has not been established. We recruited 124 lymphoma patients and analyzed the SSTR2, 3 and 5 status from their tissue samples. In addition, 21 patients underwent SSTR-targeted imaging with ^{68}Ga-DOTANOC PET/CT. The expression of chemokine receptor CXCR4, another potential molecular target candidate, was also analyzed from the tissue samples of 103 lymphoma patients.

Hodgkin lymphomas, follicular lymphomas and diffuse large B-cell lymphomas express SSTRs and CXCR4 in malignant cells, whereas mantle cell lymphomas, MALT lymphomas and peripheral T-cell lymphomas are generally SSTR and CXCR4 negative. SSTR-expressing lymphomas can be visualized on ^{68}Ga-DOTANOC PET/CT and may be amenable to SSTR-based treatment in the future.

Epidemiological studies on different lymphoma subtypes are essential, e.g., in search for underlying etiological factors contributing to lymphoma development. The epidemiology of Hodgkin lymphoma (HL) and its five subtypes in Finland in 1996–2015 was analyzed to gain a better understanding of the heterogeneity of HLs clinical behavior. Nodular sclerosis classical HL is the most common HL subtype in Finland, with a female predominance and median age of 28, whereas other HL subtypes have a male predominance and median age close to 50–60 years. Nodular lymphocyte predominant HL accounts for 13% of all HLs and is therefore more common than generally suspected.

KEYWORDS: Hodgkin lymphoma, non-Hodgkin lymphoma, somatostatin receptors, chemokine receptor CXCR4, immunohistochemistry, DOTANOC, PET/CT, incidence, mortality

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TIIVISTELMÄ

Lymfoomat jaetaan nykyisin ”kypsiin B-solukasvaimiin” ja ”kypsiin T- ja NK-solukasvaimiin” (ennen non-Hodgkin lymfoomat) sekä Hodgkin lymfoomiin, joissa on yli 60 toisistaan eroavaa alatyyppiä. Jatkuvasti kehittyvä luokittelu, taudin biologinen monimutkaisuus sekä diagnostiikan haasteellisuus ovat arkea lymfoomia diagnosoiville ja hoitaville kliinikoille.

Somatostatiinireseptoreihin (SSTR) perustuvia kuvantamis- ja hoitomuotoja voidaan käyttää sellaisten kasvainten diagnostiikassa ja hoidossa, jotka ilmentävät somatostatiinireseptoreita. Selkeää käsitystä somatostatiinireseptoreiden kliinisestä merkityksestä lymfoomissa ei kuitenkaan ole ollut. Tutkimukseen rekrytoitiin 124 lymfoomapotilasta, joiden kudosnäytteistä analysoitiin SSTR2, 3 ja 5 ilmentyminen immunohistokemiallisesti. Lisäksi 21 potilaalle tehtiin ^{68}Ga-DOTANOC PET/TT. 103 potilaan kudosnäytteistä analysoitiin myös kemokiinireseptori CXCR4 ilmentyminen, joka on toinen mahdollinen kohdemolekyyli lymfoomien diagnostiikan ja hoidon kehittämisessä.

SSTR2- ja CXCR4-reseptoreita ilmentyy erityisesti diffuusissa suurisoluisessa B-solulymfoomassa, follikulaarisesssa lymfoomassa sekä Hodgkin lymfoomassa. Somatostatiinireseptoreita ilmentävät lymfoomat näkyvät positiivisina ^{68}Ga-DOTANOC PET/TT:ssä mahdollistaen somatostatiinireseptoreihin kohdistuvien kuvantamis- ja hoitomuotojen kehittämisen tulevaisuudessa.

Epidemiologinen tutkimus lymfooman eri alatyypeistä voi auttaa selvittämään etiologisia tekijöitä lymfooman kehittymisen taustalla ja auttaa ymmärtämään taudin biologista monimutkaisuutta. Tutkimuksessa analysoitiin Hodgkin lymfooman viiden eri alatyypin epidemiologiaa Suomessa vuosina 1996–2015. Hodgkin lymfooman yleisin alatyyppi on sidekudoskyhmyinen klassinen Hodgkin lymfooma, joka on yleisempi naisilla ja keski-ikä sairastuneilla on 28 vuotta. Muut Hodgkin lymfooman alatyypit ovat yleisempiä miehillä ja niiden keski-ikä noin 50–60 vuotta. Ei-klassinen Hodgkin lymfooma (nodulaarinen runsaslymfosyyttinen) on Suomessa kolmanneksi yleisin alatyyppi (13 %), ollen siten tavanomaisesti luultua yleisempi.

AVAINSANAT: Hodgkin lymfooma, non-Hodgkin lymfooma, somatostatiini-reseptorit, kemokiinireseptori CXCR4, immunohistokemia, DOTANOC, PET/TT, ilmaantuvuus, kuolleisuus

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Abbreviations

aa-IPI	Age-adjusted international prognostic index
ABC	Activated B-cell-like
ALK	Anaplastic lymphoma kinase gene
APC	Average annual percent change
CHL	Classic Hodgkin lymphoma
CI	Confidence interval
CNS	Central nervous system
CXCR4	C-X-C chemokine receptor 4
DLBCL	Diffuse large B-cell lymphoma
DOTANOC	DOTA-1NaI3-Octreotide
DOTATATE	DOTA-Tyr3-Octreotate
DOTATOC	DOTA-Tyr3-Octreotide
EBV	Epstein-Barr virus
FCR	Finnish Cancer Registry
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
FLIPI	Follicular lymphoma international prognostic index
GCB	Germinal center B-cell-like
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HRS	Hodgkin/Reed-Sternberg
ICD-O-3	International classification for diseases of oncology 3
IHC	Immunohistochemistry
IPI	International prognostic index
LP	Lymphocyte predominant
MALT	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
MCL	Mantle cell lymphoma
MIPI	Mantle cell International Prognostic Index
MOTNAC	Manual of Tumor Nomenclature and Coding
MRI	Magnetic resonance imaging

NET	Neuroendocrine tumor
NHL	Non-Hodgkin lymphoma
NLPHL	Nodular lymphocyte predominant Hodgkin lymphoma
NOS	Not otherwise specified
OS	Overall survival
PET/CT	Positron emission tomography/computed tomography
PFS	Progression-free survival
PRRT	Peptide receptor radionuclide therapy
PTCL	Peripheral T-cell lymphoma
SLL	Small lymphocytic lymphoma
SSTR	Somatostatin receptor
SUV	Standardized uptake value
THRLBCL	T-cell/histiocyte rich diffuse large B-cell lymphoma
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Ruuska T, Ramírez Escalante Y, Vaittinen S, Gardberg M, Kiviniemi A, Marjamäki P, Kemppainen J, Jyrkkiö S, Minn H. Somatostatin receptor expression in lymphomas: a source of false diagnosis of neuroendocrine tumor at 68Ga-DOTANOC PET/CT imaging. Acta Oncol, 2018; 57:283–289.

II Juntikka, T* and Vaittinen, S*, Vahlberg T, Jyrkkiö S, Minn H. Somatostatin receptors and chemokine receptor CXCR4 in lymphomas: a histopathological review of six lymphoma subtypes. Front Oncol. 2021; 11: 710900.

III Juntikka T, Malila N, Hakanen T, Merikivi M, Jyrkkiö S. Epidemiology of Classical and Nodular Lymphocyte Predominant Hodgkin Lymphoma in Finland in 1996–2015. Acta Oncol, 2020; 59: 574–581.

*These authors contributed equally to the publication.

1 Introduction

Lymphomas are malignant tumors of the immune system with a wide range of clinical manifestations. Lymphomas can affect practically any tissue of the human body, although most of them occur in lymph nodes, causing the most common clinical presentation of painless lymphadenopathy. Disease aggressivity and prognosis varies greatly in lymphomas; some are indolent and others highly aggressive, depending on the specific lymphoma subtype in question. (Armitage et al. 2017)

The etiology of lymphomas is mostly unknown, although several risk factors have been identified. The diagnosis is based on immunohistochemical analysis of tumor biopsy. PET/CT is used for staging, and prognostic scoring provides guiding in the correct treatment selection. (Armitage et al. 2017)

New molecular and genetic features have emerged that affect in the pathogenesis of lymphomas, and are thus potential targets for developing new diagnostic and treatment methods ("theranostics"). A case of diffuse large B-cell lymphoma (DLBCL) was shown to express somatostatin receptors (SSTRs) sufficiently to cause a pitfall in the differential diagnosis of neuroendocrine tumors (NETs) at ^{68}Ga-DOTANOC PET/CT (Jain et al. 2014), which is an imaging method used to diagnose SSTR-expressing tumors such as NETs (Bozkurt et al. 2017). Hence some lymphomas could express SSTRs sufficiently to be exploited in their diagnostic and treatment. Nevertheless, the clinical significance of SSTRs in lymphomas remains unclarified (Ferone et al. 2005).

Lymphomas are highly sensitive to radiation treatment (Chan et al. 2011), and if SSTRs are found in lymphomas even in lower number than in NETs, they could potentially be used as targets for peptide receptor radionuclide therapy (PRRT), causing "internal radiation" to the lymphoma tumor (Kwekkeboom & Krenning. 2002). Another similar receptor is chemokine receptor CXCR4, which is associated with more aggressive and metastatic disease in a wide range of tumors including some malignant lymphomas (Moreno et al. 2015). As CXCR4-based imaging and treatment methods already exists, it may serve as a theranostic target also in lymphomas which express CXCR4 (Buck et al. 2017).

Epidemiological studies investigating the evolution taking place in the incidence and mortality of specific lymphoma subtypes can help identify etiological factors that contribute to lymphoma development (Morton et al. 2006). In the best case, these etiological factors could be harnessed as new targets for treatment. For example, in Hodgkin lymphomas (HLs), the clinical significance of the five different subtypes in not fully understood. Knowledge on the epidemiological patterns of HL subtypes could elucidate the biological heterogeneity and clinical significance of the subtypes.

2 Review of the Literature

2.1 Classification of lymphomas

Classification of diseases is essential; diseases cannot be diagnosed, treated or studied unless they have names. Attempts have been made to classify lymphomas for over a century, with multiple different classifications developed in recent decades (Swerdlow & Cook. 2020). Lymphomas have historically been divided into non-Hodgkin lymphomas (NHLs) and Hodgkin lymphomas (HLs) as is preferred in this doctoral thesis.

Currently, pathologists around the world use the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised Fourth Edition (Swerdlow et al. 2017) as a consensus guideline when diagnosing malignant lymphomas. The classification describes all existing lymphoma subtypes with information on their morphology, immunophenotype, genetic changes and clinical features to help clinicians in diagnosing the correct lymphoma subtype. In the WHO classification, NHLs have been replaced by "mature B-cell neoplasms" and "mature T- and NK-cell neoplasms" according to the cell of origin, with over 60 subtypes (Table 1) (Swerdlow et al. 2017).

HLs are further classified into nodular lymphocyte predominant HL (NLPHL) and classic HL (CHL). CHL includes four further subtypes and, as knowledge continues to grow, also these subtypes are increasingly being considered as different disease entities (Wang et al. 2019), creating challenges for clinicians and pathologists in the search for specific diagnosis and treatment. The four CHL subtypes are nodular sclerosis CHL, mixed cellularity CHL, lymphocyte-rich CHL, and lymphocyte-depleted CHL.

2.1.1 Cancer registries

Another type of classification is used at cancer registries around the world, which collect and report data on new cancer cases, incidence (per 100 000 person years) and mortality (per 100 000 person years). Cancer registries can be either local or population-based, covering all ages or only a subgroup. The classification or "coding" of lymphomas is essential for cancer registries, and many different

guidelines have existed for decades. (Clarke et al. 2006; Fritz et al. 2013; Gavin et al. 2015; Sant et al. 2010)

The newest and most widely adopted guideline for coding the morphology, topography, and behavior of hematological and lymphoid malignancies is the International Classification of Diseases for Oncology, 3rd Edition 2001 (ICD-O-3), and its first revision (ICD-O-3.1) from 2011 (Fritz et al. 2013). ICD-O-3 is the first coding manual directed at cancer registries in which the codes incorporate the WHO classification used in clinical practice (Clarke et al. 2006), making ICD-O-3 is the first feasible guideline for cancer registries. (Fritz et al. 2013; Morton et al. 2006)

The WHO 2016 and ICD-O-3 classifications of NHLs are shown in Table 1.

Table 1. Classification of NHL main subtypes according to WHO 2016 and ICD-O-3 and their percentual proportion, if applicable (modified from Swerdlow et al. 2017).

WHO 2016	ICD-O-3	Proportion
Precursor lymphoid neoplasms		
B-lymphoblastic leukemia/lymphoma, NOS	M9811/3	
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities	M9812/3 to M9819/3	
T-lymphoplastic leukemia/lymphoma	M9837/3	
NK-lymphoplastic leukemia/lymphoma		
Mature B-cell neoplasms		
Chronic lymphocytic leukemia/small lymphocytic lymphoma	M9823/3	7% of all NHLs
B-cell lymphocytic leukemia	M9833/3	1% of all lymphocytic leukemias
Splenic marginal zone lymphoma	M9689/3	< 2% of lymphomas
Hairy cell leukemia	M9940/3	2% of lymphomas
Splenic B-cell lymphoma/leukemia, unclassifiable	M9591/3	
Lymphoplasmacytic lymphoma	M9671/3 (and M9761/3 for WM)	
IgM monoclonal gammopathy of undetermined significance	M9761/1	
Heavy chain diseases	M9762/3	
Plasma cell neoplasms	M9765/1 M9732/3 M9731/3 M9734/3 M9769/1 M9769/1	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	M9699/3	7–8% of all B-cell lymphomas
Nodal marginal zone lymphoma	M9699/3	1.5–1.8% of all lymphoid neoplasms

WHO 2016	ICD-O-3	Proportion
Follicular lymphoma	M9690/3 M9695/1 M9695/3	20% of all lymphomas
Pediatric-type follicular lymphoma	M9690/3	
Large B-cell lymphoma with IRF4 rearrangement	M9698/3	0.05% of all DLBCLs
Primary cutaneous follicle center lymphoma	M9597/3	50% of all primary cutaneous B-cell lymphomas
Mantle cell lymphoma	M9673/3	3–10% of all NHLs
Diffuse large B-cell lymphoma, NOS	M9680/3	25–30% of adult NHLs in developed countries
T-cell/histocyte-rich large B-cell lymphoma (THRLBCL)	M9688/3	< 10% of all DLBCLs
Primary diffuse large B-cell lymphoma of the CNS	M9680/3	< 1% of all NHLs
Primary cutaneous diffuse large B-cell lymphoma, leg type	M9680/3	20% of all primary cutaneous B-cell lymphomas
EBV-positive diffuse large B-cell lymphoma, NOS	M9680/3	< 5% of all DLBCLs in Western countries
EBV-positive mucocutaneous ulcer	M9680/1	
Diffuse large B-cell lymphoma associated with chronic inflammation	M9680/3	
Lymphomatoid granulomatosis	M9766/3	
Primary mediastinal (thymic) large B-cell lymphoma	M9679/3	2–3% of all NHLs
Intravascular large B-cell lymphoma	M9712/3	
ALK-positive large B-cell lymphoma	M9737/3	< 1% of DLBCLs
Plasmablastic lymphoma	M9735/3	
Primary effusion lymphoma	M9678/3	
HHV8-associated lymphoproliferative disorders	M9738/3 M9738/1	
Burkitt lymphoma	M9687/3	1–2% of all lymphomas in Western Europe and USA
Burkitt-like lymphoma with 11q aberration	M9687/3	
High-grade B-cell lymphoma	M9680/3	
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma (cHL), “grey zone lymphoma”	M9596/3	
Mature T- and NK-cell neoplasms		
T-cell prolymphocytic leukemia	M9834/3	2% of all mature lymphocytic leukemias in adults
T-cell large granular lymphocytic leukemia	M9831/3	2–3 % of mature small lymphocytic leukemias
Chronic lymphoproliferative disorder of NK cells	M9831/3	
Aggressive NK-cell leukemia	M9948/3	
EBV-positive T-cell and NK-cell lymphoproliferative diseases of childhood	M9724/3 M9725/1	
Adult T-cell leukemia/lymphoma	M9827/3	
Extranodal NK/T-cell lymphoma, nasal type	M9719/3	

WHO 2016	ICD-O-3	Proportion
Intestinal T-cell lymphoma	M9717/3 M9702/1	
Hepatosplenic T-cell lymphoma	M9716/3	
Subcutaneous panniculitis-like T-cell lymphoma	M9708/3	
Mycosis fungoides	M9700/3	50% of all primary cutaneous lymphomas
Sezary syndrome	M9701/3	< 5% of all cutaneous T-cell lymphomas
Primary cutaneous CD30-positive T-cell lymphoproliferative disorders	M9718/1 M9718/3	
Primary cutaneous peripheral T-cell lymphomas, rare subtypes	M9726/3 M9709/3 M9709/3 M9709/1	
Peripheral T-cell lymphomas, NOS	M9702/3	30% of all peripheral T-cell lymphomas in western countries
Angioimmunoblastic T-cell lymphoma and other nodal lymphomas of T-follicular helper cell origin	M9705/3 M9702/3	
Anaplastic large cell lymphoma, ALK-positive	M9714/3	3% of adult NHLs, 10–20% of childhood lymphomas
Anaplastic large cell lymphoma, ALK-negative	M9715/3	
Breast implant-associated anaplastic large cell lymphoma	M9715/3	

NOS=not otherwise specified
CNS=central nervous system
IRF4=interferon regulatory factor 4
EBV=Epstein-Barr virus
ALK=anaplastic lymphoma kinase
HHV-8=human herpes virus 8
NK=natural killer

As with the WHO classification, also the coding protocols for cancer registries are under constant change and development. For example, when the population-based Finnish Cancer Registry (FCR) was founded in 1952, they adopted a modified version of the Manual of Tumour Nomenclature and Coding (MOTNAC 1953) classification for morphology, and the International Classification of Diseases, Revision 7 (ICD-7 1955) for topography as their coding manual (Table 2). (Finnish Cancer Registry 2021) At the time, the "Hodgkin NOS" code was used for all HL cases, clearly. When the ICD-O-3 classification was taken into use in 2007 at the FCR, all HL subtypes were entered with individual codes into the FCR database. This meant having to re-code all prior HL NOS cases into more specific matching ICD-O-3 codes to enable longer-term statistics on HL subtypes. (Leinonen et al. 2018) Some re-coding is being done at the FCR by epidemiological cancer studies needing long-term statistics for their analyses, and on an individual basis by FCR

staff if a patient has new cancer and the previous one came under the old classification. Changing coding guidelines create significant challenges for cancer registries.

Table 2. Classification of Hodgkin lymphomas according to WHO 2016, ICD-O-3 and MOTNAC.

WHO 2016 (Pathologists)	**ICD-O-3** (FCR* after 2007)	**MOTNAC** (FCR* 1953–2007)
Hodgkin lymphoma NOS*	M9650/3	32.8
Nodular sclerosis classic Hodgkin lymphoma	M9663/3	32.8
Mixed cellularity classic Hodgkin lymphoma	M9652/3	32.8
Lymphocyte-rich classic Hodgkin lymphoma	M9651/3	32.8
Lymphocyte-depleted classic Hodgkin lymphoma	M9653/3	32.8
Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)	M9659/3	32.8

* FCR, Finnish Cancer Registry.
**NOS, not otherwise specified

Since knowledge on HL as a disease entity has grown vastly since the 1950's, it is clear that coding manuals at cancer registries need to evolve and change over time. A new update of the ICD-O-3 (version 2, ICD-O-3.2) is soon to be published (IACR 2021).

2.1.2 WHO 2016 revision

The classification of lymphomas is constantly under revision as new information is acquired and new subtypes are recognized (Swerdlow et al. 2016). The WHO Classification was last revised in 2016. The main updates in the WHO 2016 revision (compared to the previous version from 2008) are listed in Table 3 for DLBCL, FL, MCL, MALT, and PTCL (Choi & O'Malley 2018; Leonard et al. 2017; Li et al. 2018; Quintanilla-Martinez 2017; Swerdlow et al. 2016).

Table 3. WHO 2016 updates on the classification of DLBCL, FL, MCL, MALT and PTCL (modified from Choi & O'Malley 2018; Leonard et al. 2017; Li et al. 2018; Quintanilla-Martinez 2017 and Swerdlow et al. 2016).

CHANGE TO CLASSIFICATION:
Large cell lymphoma with IRF4/MUM1 rearrangement was added as a provisional entity.
The identification of germinal center B-cell-like (GBC) and activated B-cell-like (ABC) subtypes is required in the classification of DLBCL.
High-grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6 was added ("double-hit" and "triple-hit" lymphomas).
"EBV-positive DLBCL, NOS" replaced the old "EBV-positive DLBCL of the elderly" as EBV-positive DLBCL has been recognized in younger patients also.
EBV-positive mucocutaneus ulcer has been added as a provisional entity.
Three new variants of FL were added: duodenal-type follicular lymphoma, testicular follicular lymphoma, and diffuse follicular lymphoma variant.
Pediatric type follicular lymphoma was added.
Two MCL subtypes are recognized: classical MCL and leukemic non-nodal MCL.
Classification of intestinal T-cell lymphomas, anaplastic large cell lymphomas and nodal T-cell lymphomas was modified.

IRF4/MUM1= Interferon regulatory factor 4 / multiple myeloma 1 protein
MYC=MYC proto-oncogene gene/protein
BCL2=B-cell lymphoma 2 gene/protein
BCL6=B-cell lymphoma 6 gene/protein
DLBCL=diffuse large B-cell lymphoma
NOS= not otherwise specified
EBV=Epstein-Barr virus
FL=follicular lymphoma
MCL=mantle cell lymphoma

The classification of HL subtypes remained unchanged in the WHO 2016 revision, with some additions made instead (Jiang et al. 2017; Swerdlow et al. 2017) (Table 4).

Table 4. WHO 2016 updates on the classification of HLs (modified from Jiang et al. 2017).

HL subtype	**Addition to classification**
Lymphocyte-rich	Recognition of features intermediate between CHL and NLPHL
NLPHL	Histologic pattern should be specified when known (variant pattern is associated with more aggressive behavior).
	Cases with THRLBCL-like features should be called THRLBCL-like transformation of NLPHL (to distinguish from true THRLBCL).

CHL=classic Hodgkin lymphoma
NLPHL=nodular lymphocyte predominant Hodgkin lymphoma
THRLBCL= T-cell/histiocyte rich diffuse large B-cell lymphoma

2.2 Non-Hodgkin lymphoma

NHLs represent 90% of all lymphomas. They can be derived from either B-cells, natural killer cells (NK-cells), or T-cells at various stages of differentiation. There are over 40 major NHL subtypes with different morphological and clinical characteristics, making diagnostics truly challenging for clinicians. (Chihara et al. 2015; Shankland et al. 2012)

Of main interest in this doctoral thesis are the following five NHL subtypes: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), and peripheral T cell lymphoma (PTCL).

2.2.1 Etiology

There are several known risk factors for NHL (Table 5), although the etiology of most NHLs remains unknown (Armitage et al. 2017; Chihara et al. 2015; Chiu & Hou 2015).

Table 5. Risk factors for non-Hodgkin lymphomas.

FACTOR	Complementary information
Acquired or congenital immunosuppression	i.e. HIV infection increases the risk of NHL 75–100-fold
Immunosuppressive drugs following organ transplantations (solid or stem cell)	30–50-fold risk of NHL especially during the first year after transplant
Chemotherapy and radiation	Increased risk of secondary NHL
Autoimmune diseases	Celiac disease, inflammatory bowel disease, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus
Viruses	i.e. EBV, hepatitis C virus, Kaposi sarcoma-associated herpesvirus, human T-cell lymphotropic virus
Bacterial infections	i.e. Helicobacter pylori (causes gastric MALT lymphoma), and borrelia burgdorferi (primary cutaneous B-cell lymphoma)
Genetic factors	i.e. genetic variants that promote B-cell survival and growth
Dietary factors	Increased meat, fat and sugary consumption
Obesity	Increased risk of DLBCL and FL
Extensive smoking	Increased risk of FL and PTCL
Chemicals	i.e. hair dyes
Occupational risk	i.e. exposure to pesticides

HIV=human immunodeficiency virus
NHL=non-Hodgkin lymphoma
EBV=Epstein-Barr virus
MALT=extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
DLBCL=diffuse large B-cell lymphoma
FL=follicular lymphoma
PTCL=peripheral T-cell lymphoma

2.2.2 Epidemiology

NHL is the 5th to 9th most common cancer in the world and it is the most common hematological malignancy. Creating reliable universal statistics is challenging, since the incidence of different NHL subtypes varies markedly between geographical areas, age, gender, and ethnicity, and also the quality of cancer registries reporting incidence statistics also varies. (Chihara et al. 2015; Ferlay et al. 2013; Miranda-Filho et al. 2019)

NHL is more common in developed countries compared to developing areas (Chihara et al. 2015). In developing countries, there is a lower frequency of B-cell lymphomas (but more cases are high-grade) and a higher frequency of NK/T-cell lymphomas compared to developed countries (Perry et al. 2016).

DLBCL and FL are the most common NHL subtypes in Western countries (Table 6). Males are most often affected by NHL, with the peak incidence after 75 years of age. The age-adjusted incidence rate of NHL in Europe is 13.5/100 000 person years in males and 9.7/100 000 in females. (Chihara et al. 2015; Ferlay et al. 2013; Miranda-Filho et al. 2019)

In Europe, the incidence of NHL rose until the 1990's before leveling off, but the mortality of NHL has been declining and is roughly 4.1/100 000 person years in males and 2,5/100 000 in females, respectively (Bosetti et al. 2008). Survival has continued to improve in Europe in recent decades, probably due to improved diagnostic and treatment methods, but there are still some major differences between NHL subtypes: age-standardized 5-year relative survival is 55.4% in DLBCL and 74.3% in FL (in 2006–2008) (Molina 2008; Sant et al. 2014). Prognosis in peripheral T-cell lymphomas is generally poor, with a 5-year overall survival of 20–30% in PTCL, NOS (Oluwasanjo et al. 2019). Some exceptions do occur: 5-year survival is 79% in ALK-positive anaplastic large cell lymphoma compared with 46% in ALK-negative anaplastic large cell lymphoma (Zain 2019).

Table 6. Epidemiology of DLBCL, FL, MCL, MALT and PTCL in Western countries (Chihara et al. 2015; Dada 2019; Dreyling et al. 2016; Foss et al. 2011; Freedman & Jacobsen 2020; Li et al. 2018; Oluwasanjo et al. 2019; Raderer, Kiesewetter, & Ferreri 2016; Smedby & Hjalgrim 2011; Swerdlow et al. 2017; Vose 2017).

Subtype	Incidence (/100 000)	Survival	Median age	Typical characteristics
DLBCL	4–7	5-y OS 60–70%	70 y	Most common NHL in the world. Slightly more common in males than in females. Aggressive.
FL	5	10-y OS approximately 80%	60–65 y	More common in females (M:F ratio 1:1.7). Generally indolent. Presents with chronic relapsing.
MCL	0,5–2	Median OS 4–5 y	60–70 y	More common in males (M:F ratio 3:1). Aggressive.
MALT	0,4–1	5-y OS >90%	65 y	Slightly more common in females in selected sites. Indolent.
PTCL	<1	5-y OS 20–30%	60–70 y	M:F ratio 2:1. Highly aggressive. Presents with advanced stages, poor response to therapy and frequent relapses.

DLBCL=diffuse large B-cell lymphoma
FL=follicular lymphoma
MCL=mantle cell lymphoma
MALT=extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
PTCL=peripheral T-cell lymphoma
OS=overall survival
M:F=male to female ratio

2.2.3 Diagnostics

The diagnostics of NHL are based on morphological, immunohistochemical and genetic analysis of tissue sample biopsies (core or excisional). A whole lymph node biopsy is preferred. Fine needle aspirates are not sufficient for diagnosis. Other examinations include physical examination, blood work-up (including tests for HIV and hepatitis B and C), bone marrow biopsy (preferable especially in low-stage NHLs such as FL), ultrasound, computed tomography (CT) or positron emission tomography (PET)/CT, endoscopy, and in some cases even MRI or lumbar puncture. Cardiac function should be assessed prior to any treatment. (Dada 2019; Dreyling et al. 2017; Tilly et al. 2015)

2.2.3.1 Clinical features

Indolent NHLs typically present with painless lymphadenopathy. Systemic symptoms and symptoms caused by extranodal lesions are more common in advanced and aggressive NHLs, such as DLBCL and MCL. One-third of patients

with aggressive NHLs experience B-symptoms, which include fever, night sweats and weight loss of over 10 % in 6 months. Extranodal lesions (i.e., bone marrow, skin, gastrointestinal tract, CNS) can cause a wide variety of symptoms. Bone marrow involvement can cause cytopenias. (Ansell 2015)

2.2.3.2 Histopathology

The typical immunohistochemical and genetic features of DLBCL, FL, MCL, MALT, and PTCL are presented in Table 7 (Li et al. 2018; Liu & Barta 2019; Raderer et al. 2016; Swerdlow et al. 2017; Vose 2017).

Table 7. Immunohistochemical and genetic features of lymphomas.

Subtype	Immunohistochemistry	Genetic profile
DLBCL	Positive for CD19, CD20, CD22, CD79a, PAX5 and cytoplasmic or surface immunoglobulin (IgM, IgG, IgA) Negative for pan T-cell antigens Variable expression of CD5, CD10, CD30, MYC, BCL2, BCL6, IRF4/MUM1, FOXP1, GCET1, LMO2, PDL1/L2, p53 and EBV High Ki-67 proliferation index (more than 40% but can reach >90%)	Clonally rearranged IG heavy and light chains Translocations of MYC (in 8–14%), BCL2 (in 20–30%), and BCL6 (in 30%). Roughly 50% of the MYC translocated DLBCLs also harbor BCL2 and/or BCL6 translocation (these are classified as high-grade B-cell lymphomas) Mutations in EZH2, GNA13, PTEN (GCB subtype) and CARD11, MYD88 and CD79B (ABC subtype)
FL	Positive for BCL2, CD19, CD20, CD22, CD79a, CD10, BCL6, and surface immunoglobulin Negative for CD5 and CD43 Variable expression of CD21, CD23, and IRF4/MUM1 Ki-67 proliferation index <20% in grade 1 and 2 FL, and >20% in grade 3 FL	Rearranged IG heavy and light chains BCL2 translocated or mutated in 85–90%. Occasionally BCL-6 translocation in high-grade FL Mutations in KMT2D, TNFRSF14, EZH2, EPHA7, CREBBP
MCL	Positive for surface IgM/IgD, BCL2, Cyclin D1, and SOX11 Variable expression of CD5, FMC7, CD43, IRF4/MUM1 Usually negative for CD10 and BCL6. Mainly negative for CD23. Note: SOX11 is negative in indolent forms.	Clonally rearranged IG genes. Genetic alterations in 3q26, 7p21, 1p13-31, 13q11-13, 13q14-34, Cyclin D1, MYC, TNFAIP3, CDKN2A, ATM and TP53

Subtype	Immunohistochemistry	Genetic profile
MALT	Positive for CD20, CD79a, and IgM (less often IgG or IgA) Negative for CD5, CD10, and CD23 Variable expression of CD43 and CD11c	Rearranged IG heavy and light chains Chromosomal translocations of t(11;18), (q21;q21), t(1;14)(p22;q32), t(14;18), (q32;q21), and t(3;14)(p14.1;q32) Production of BIRC3-MALT1 protein. Transcriptional regulation of BCL10, MALT1, and FOXP1
PTCL	Positive for beta F1 Downregulation of CD5 and CD7. CD4+/CD8- phenotype in nodal cases. CD4/CD8 double negativity or double positivity also possible Variable expression of CD8, CD15, CD20, CD30, CD52, CD56, CD79a, cytotoxic granules, TBX21, and GATA3 Usually high Ki-67 proliferation index	T-cell receptor genes clonally rearranged Complex karyotypes and recurrent chromosomal gains and losses

DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; MCL=mantle cell lymphoma; MALT=extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; PTCL=peripheral T-cell lymphoma; IG=immunoglobulin; PAX5=paired box 5 gene/protein; BCL2=B-cell lymphoma 2 gene/protein; BCL6=B-cell lymphoma 6 gene/protein; MYC=MYC proto-oncogene gene/protein, IRF4/MUM1= interferon regulatory factor 4 / multiple myeloma 1 protein; FOXP1= forkhead box P1 gene/protein; GCET1= germinal center B cell-expressed transcript-1 protein; LMO2=LIM domain only 2 gene/protein; PDL1/L2=programmed death ligand 1/2 protein; EBV=Epstein-Barr virus; EZH2=enhancer of zeste homolog 2 ; GNA13= guanine nucleotide-binding protein subunit alpha-13; PTEN= phosphatase and tensin homolog; GCB=germinal center B-cell-like; CARD11= caspase recruitment domain family, member 11; MYD88= myeloid differentiation factor 88; ABC=activated B-cell-like; KMT2D=lysine methyltransferase 2D; TNFRSF14=tumor necrosis factor receptor superfamily member 14 gene/protein; EPHA7=ephrin type-A receptor 7 gene/protein; CREBBP=CREB binding protein; TNFAIP3=TNF alpha induced protein 3 gene; CDKN2A=cyclin-dependent kinase inhibitor 2A gene; TP53=tumor protein p53 gene; MALT1= mucosa-associated lymphoid tissue lymphoma translocation 1 gene; BIRC3=baculoviral IAP repeat-containing 3 gene; TBX21= T-Box transcription factor 21

Since the publication of the WHO 2016 classification, new information has been learned on NHL subtypes. For example, four genetic subtypes of DLBCL have been identified (Schmitz et al. 2018). The constantly evolving field of NHL subtypes creates significant challenges for pathologists and clinicians diagnosing and treating lymphomas.

2.2.3.3 PET/CT imaging

^{18}F-Fluoro-Deoxy-Glucose (^{18}F-FDG) Positron Emission Tomography (PET) combined with computed tomography (CT), henceforth "FDG PET/CT", is the gold standard in diagnosing and staging FDG-avid NHLs and in end-of-treatment evaluation of treatment response. Interim FDG PET/CT can be used in some cases for evaluating treatment response, but the role is not well established. (Armitage et al. 2017; Barrington et al. 2014; Zelenetz et al. 2016) DLBCL, FL, and MCL are highly FDG avid (97–100%), but MALT lymphoma only in 54–81% and peripheral T-cell lymphomas in 86–98% of patients (Barrington et al. 2014).

The performance of FDG PET/CT scans is standardized in accordance with European Association of Nuclear Medicine (EANM) procedure guidelines (Boellaard et al. 2015). The preferred method for reporting tumors metabolic activity in interim and end-of-treatment FDG-PET/CT is a 5-point scale called the Deauville score, where ≥3 points is generally regarded as PET-positive (Table 8) (Cheson et al. 2014). The Deauville score has been validated in most lymphoma subtypes where a good interobserver agreement has been reported, although addition of semi-quantitative methods based on standardized uptake values (SUVs) improves the agreement (Barrington & Kluge 2017; Dupuis et al. 2012; Itti et al. 2013). To minimize false-positive findings, the guideline is to perform scans at least 10 days after the last chemotherapy cycle and 3 months after radiation therapy, but also 2 weeks after final administration of granulocyte colony-stimulating factor therapy (Boellaard et al. 2015).

Table 8. Deauville score for evaluating tracer uptake and metabolic response at interim and end-of-treatment FDG PET/CT. (Modified from Zaucha et al. 2019 and Barrington et al. 2017)

Deauville score	Uptake
1	No
2	Below or equal to mediastinum
3	Below mediastinum but lower or equal to liver
4	Moderately higher than liver
5	Markedly higher than liver and/or new lesions

2.2.3.4 Ann Abor staging and prognostic indexes

After performing FDG PET/CT as a baseline study, NHLs are staged according to the Ann Arbor classification system (Table 9). The prognosis is thereafter evaluated by the international prognostic scores presented in Tables 10 and 11. A risk stratification score is available also for MCL but is not presented here (Mantle cell International Prognostic Index, MIPI) (Dreyling et al. 2017). Although the International Prognostic Index (IPI) was developed in 1993 (International Non-

Hodgkin's Lymphoma Prognostic Factors Project, 1993), it was also validated during the rituximab era and remains the recommended prognostic tool in DLBCL and PTCL (Armitage et al. 2017; d'Amore et al. 2015; Tilly et al. 2015; Ziepert et al. 2010)

Table 9. Ann Arbor staging with Cotswold modifications. (Modified from Townsend et al. 2012)

Stage	Description
I	Involvement of one lymph-node region or lymphoid structure
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph nodes on both sides of the diaphragm
IV	Involvement of extranodal sites other than one contiguous or proximal extranodal site
Modifying features	
A	No B-symptoms
B	Presence of B-symptoms (fever, drenching night sweats, loss of more than 10% of bodyweight) over 6 months
E	Involvement of one contiguous or proximal extranodal site

Table 10. International prognostic index (IPI), age-adjusted IPI (aa-IPI), and the prognosis according to score in DLBCL (Modified from Tilly et al. 2015).

IPI risk factors (1 point for each)	
Age > 60 years	
Serum LDH* elevated	
Ann Arbor stage > II	
Performance status 2–4	
Number of extranodal sites > 1	
Prognosis	
IPI points (risk category)	**Estimated 3-year OS (%)**
0–1 (low)	91
2 (low intermediate)	81
3 (high intermediate)	65
4–5 (high)	59
aa-IPI risk factors in patients ≤ 60 years (1 point for each)	
Serum LDH* elevated	
Ann Arbor stage > II	
Performance status 2-4	
Prognosis	
aa-IPI points (risk category)	**Estimated 3-year OS (%)**
0 (low)	98
1 (low intermediate)	92
2 (high intermediate)	75
3 (high)	75

*LDH=lactate dehydrogenase

Table 11. Follicular lymphoma international prognostic index (FLIPI) and the prognosis according to score in the rituximab era (Modified from Dada et al. 2019).

FLIPI (1 point for each characteristic described below)	
Age > 60 years	
Serum LDH* elevated	
Hemoglobin level < 120 g/l	
Ann Arbor stage > II	
Number of involved nodal areas > 4	
Prognosis	
FLIPI score (points)	**Two-year OS** (%)**
0–1	98
2	94
>3	87

*LDH=lactate dehydrogenase
**OS=overall survival

2.2.3.5 Pitfalls

NHLs can present in any organ, and the variety of symptoms is enormous. There is clinical and histological overlap between NHL, HL, and other hematological and lymphoid malignancies. NHLs can also mimic other diseases such as infection, sarcoidosis, and vasculitis (Yeh et al. 2020). Therefore, diagnosis of specific NHL subtype is challenging, and multiple conditions should be addressed in the differential diagnostics of NHL (Table 12). (Armitage et al. 2017)

Table 12. Differential diagnosis in non-Hodgkin lymphoma (Modified from Armitage et al. 2017).

Subtype	**Differential diagnosis**
DLBCL	Peripheral T-cell lymphoma; Burkitt-like lymphoma; lymphoblastic lymphoma; grade 3B follicular lymphoma; myeloid sarcoma; carcinoma; melanoma
FL	Follicular hyperplasia; small lymphocytic lymphoma; chronic lymphocytic leukaemia; mantle cell lymphoma; marginal zone lymphoma; lymphoplasmacytic lymphoma; nodular lymphocyte-predominant Hodgkin's lymphoma; lymphocyte-rich classic Hodgkin's lymphoma
MCL	Reactive hyperplasia; small lymphocytic lymphoma; chronic lymphocytic leukaemia; grade 1 and 2 follicular lymphomas; lymphoplasmacytic lymphoma; nodular lymphocyte-predominant Hodgkin's lymphoma; lymphocyte-rich classic Hodgkin's lymphoma
MALT	Reactive hyperplasia; small lymphocytic lymphoma; chronic lymphocytic leukaemia; follicular lymphoma (particularly those with marginal zone differentiation); nodal and splenic marginal zone lymphomas; lymphoplasmacytic lymphoma
PTCL	Florid reactive hyperplasia; T-cell-rich diffuse large B-cell lymphoma; mixed cellularity Hodgkin's lymphoma

DLBCL=diffuse large B-cell lymphoma
FL=follicular lymphoma
MCL=mantle cell lymphoma
MALT=extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
PTCL=peripheral T-cell lymphoma

In addition to challenging differential diagnostics, there are other potential pitfalls in the diagnosis of NHLs:

- Pitfalls in pathology. Inadequate, crushed, or necrotic tissue specimen, inadequate immunohistochemical or genetic studies or lack of knowledge in their interpretation, leading to incomplete or inaccurate lymphoma diagnosis. (Wilkins 2011)
- False-positive findings on FDG-PET/CT. Including infection, inflammation, reactive changes after treatment (i.e., increased activity after radiation therapy or granylocyte colony-stimulating factor therapy), degenerative changes, high physiological FDG uptake (i.e., brains, gastrointestinal tract, muscle, bladder, thymus). (Baba et al. 2011; Kazama et al. 2005)

2.2.4 Treatment

Some NHLs can be cured. Careful and accurate diagnosis, staging, and evaluation of prognosis are needed to be able to choose the correct treatment method (Ansell 2015). In elderly patients (>70 years-of-age) it is important to evaluate physical condition and quality of life and adjust the treatment selection accordingly (Buske et al. 2018). Treatment choices in NHLs vary from observation to high-dose more toxic treatments and to newer targeted therapies:

- Watch-and-wait in advanced asymptomatic FL (Dreyling et al. 2016).
- Antibiotic treatment: eradication of H. pylori in gastric MALT (Zucca et al. 2020)
- Radiotherapy and/or chemotherapy. Chemotherapy regimen including rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is the standard treatment in DLBCL (Armitage et al. 2017)
- Autologous or allogeneic stem cell transplantation both in B- and T-cell lymphomas (Dreyling et al. 2017; Kothari et al. 2014; Zain 2019)
- Radioimmunotherapy (Eskian et al. 2018)
- Newer treatment modalities such as chimeric antigen receptor T-cells (CAR-T cells) in DLBCL (Boyiadzis et al. 2018), antibody-drug conjugate Brentuximab vedotin in relapsed anaplastic large cell lymphoma (d'Amore et al. 2015; Pro et al. 2012), and B-cell receptor inhibitor Ibrutinib in MCL and in relapsed DLBCL and FL (Armitage et al. 2017).
- Maintenance treatment with rituximab in FL and MCL (Armitage et al. 2017).

2.3 Hodgkin lymphomas

HLs represent 10% of all lymphomas. They are characterized by the presence of scattered Hodgkin/Reed-Sternberg (HRS) cells surrounded by a rich inflammatory cell background and/or fibrosis. Usually, neoplastic B-cells have T-cells surrounding them with a ring-like appearance. CHLs account for roughly 90% of all HL cases and NLPHL for 5–10% of all HL cases, respectively. (Wang et al. 2019; Yung & Linch 2003)

NLPHL was first recognized as a separate disease entity in 1994 (Harris et al. 1994) and is now known to have different clinicopathological, etiological and epidemiological features compared to CHL. Even the neoplastic cells are different in NLPHL: monoclonal B-cells originating from germinal centers are called lymphocyte predominant (LP) or "popcorn cells". (Lee & LaCasce 2009).

2.3.1 Etiology

The etiology of HL remains mostly unknown (Ansell 2018). Some connection to HL development has been shown with immunosuppression, previous autoimmune conditions, HIV, and solid organ transplantation (Kristinsson et al. 2009; Shanbhag & Ambinder 2018). EBV is associated with some CHL subtypes, with the strongest association observed in mixed cellularity and lymphocyte-depleted classic HLs, where up to 75% of patients are EBV-positive. On the other hand, NLPHL has no association to EBV. (Murray & Young 2019; Swerdlow et al. 2017; Townsend & Linch 2012; Zhang et al. 2014) The presence of EBV in HL cells has been connected to poorer outcome in older nodular sclerosis CHL patients and better outcome in younger patients (Keegan et al. 2005). High socioeconomic status has been connected to higher risk of developing HL (Rafiq et al. 2019). There is also a familial risk in CHL and NLPHL, affecting especially siblings (Kharazmi et al. 2015; Saarinen et al. 2013).

2.3.2 Epidemiology

Although HL is a rare hematological malignancy accounting for only 0.4% of all new cancers worldwide (Bray et al. 2018), it is the most common lymphoma in young adults in the Western countries (Bazzeh et al. 2010; Mottok & Steidl 2018). The incidence of HL is approximately 2.2/100 000 and the mortality 0.7/100 000 person years in Europe (Eichenauer et al. 2018). The incidence has remained quite steady over the past decades, while the mortality has declined (Hjalgrim et al. 2001; Morton et al. 2006; Shanbhag & Ambinder 2018). The incidence of HL is higher in developed Western countries compared to developing countries (Cartwright & Watkins 2004).

CHL has a bimodal age distribution with the highest incidence rates in 15–35-year-olds and over 55–60-year-olds. There is a male predominance, except for nodular sclerosis CHL where young females are most often affected. (Ansell 2018; Wang et al. 2019)

The four CHL subtypes have some unique features in their etiology and epidemiology (Shanbhag & Ambinder 2018; Wang et al. 2019):

- Nodular sclerosis CHL is the most common subtype, with the incidence peak in young adults (15–34 years) and very few cases in the older population. There is a female predominance. Mediastinal adenopathy and bulky disease are common, whereas EBV positivity is not (10–25%). The prognosis is better than in mixed cellularity and lymphocyte-depleted CHL.
- Mixed cellularity CHL is the second most common subtype with incidence peaks in children and over 60-year-olds. It has high EBV-positivity and is more common in developing countries and patients with HIV.
- Lymphocyte-rich CHL accounts for 5% of CHL is found mainly in the elderly. It has features of peripheral adenopathy (rather than bulky mediastinal mass), early-stage disease, and has a good prognosis.
- Lymphocyte-depleted CHL is the rarest subtype in the Western countries, with the highest incidence in children and over 60-year-olds. It has high EBV positivity similarly to mixed cellularity CHL and is more common in developing countries and patients with HIV. It has more aggressive behavior than other CHL subtypes.

NLPHL is an even rarer disease entity than CHL with an estimated incidence of 0.1–0.2/100 000 person years. NLPHL accounts for 5–10% of all HL cases. NLPHL is usually indolent and diagnosed at early stages, with excellent prognosis. There is a clear male predominance, with the highest incidence rates at the age of 30–40 years. (Eichenauer & Engert, 2017; Wang et al. 2019)

2.3.3 Diagnostics

The diagnostics of HL are similar to those for NHLs and they are based on immunohistochemical analysis of surgically removed tissue biopsy, preferably a whole excisional lymph node. Core needle biopsy may be useful but often causes problems in the differential diagnostics. FDG-PET/CT is a routinely performed imaging method in HL. (Ansell 2018; Cheson et al. 2014).

2.3.3.1 Clinical features

CHL typically presents with painless enlarged lymph node(s) in the neck or in the mediastinum. The mediastinal masses can grow rather large (“bulky disease”) before causing any symptoms (i.e., persistent cough). B-symptoms are often present in advanced stage HL or bulky disease. Fatigue, itching, and alcohol-induced pain at the tumor sight can also occur. (Shanbhag & Ambinder 2018; Wang et al. 2019)

NLPHL is an indolent lymphoma usually presenting as a slowly growing enlarged peripheral lymph node, whereas mediastinal nodal masses are rare. Approximately 80% of patients are diagnosed in the early stages (ST I–II) and B-symptoms are uncommon. In the case of ST III–IV disease (20%), the behavior is more aggressive and up to 13% of NLPHL can transform into DLBCL. (Strobbe et al. 2016; Wang et al. 2019; Xing & Savage 2013)

2.3.3.2 Histopathology

The immunohistochemical features of HLs are presented in Table 13. Although the malignant HRS cells in all four CHLs show similarities in immunohistochemical staining, the morphology and tumor microenvironment differ in the four CHL subtypes considerably. Hence, adequate tissue biopsy material is crucial for determining the tumor architecture and the specific HL subtype. (Wang et al. 2019)

In NLPHL, scattered malignant LP cells are surrounded by a ring of T-cells and some non-neoplastic reactive B-cells and histiocytes. NLPHL typically has a nodular growth pattern with indolent behavior, but also a variant growth pattern exists (most often observed in advanced stage diseases). In the case of a variant growth pattern there is both histopathological and clinical overlap with T-cell/histiocyte rich DLBCL (THRLBCL). (Hartmann & Eichenauer, 2020; Spinner, Varma, & Advani, 2019; Wang et al. 2019)

Table 13. Immunohistochemical features of Hodgkin lymphomas. (Modified from Wang et al. 2019)

Subtype	Typical immunohistochemical findings
CHL	HRS cells usually express CD30, CD15, IRF4/MUM1, PAX5.
	Rare expression of CD20, CD45 and CD79a.
	PD-L1/2 is often overexpressed.
	Aberrant expression of T-cell markers CD2 and CD4 is connected to worse outcome.
NLPHL	Usually expression of CD20, CD45, CD79a, CD19, PAX5, OCT2, EMA, CD75, BCL6 and HGAL.
	LP cells are negative for CD15, CD30 and PD-L1/2.

CHL=classic Hodgkin lymphoma
HRS=Hodgkin / Reed-Sternberg
IRF4/MUM1= interferon regulatory factor 4 / multiple myeloma 1 protein
PAX5=paired box 5 gene/protein
PD-L1/2=programmed death ligand 1/2
OCT2=organic cation transporter 2 gene/protein
EMA=epithelial membrane antigen protein
BCL6=B-cell lymphoma 6 gene/protein
HGAL= human germinal center-associated lymphoma gene
LP=lymphocyte predominant

2.3.3.3 PET/CT imaging

CHL is a highly FDG-avid lymphoma (97–100%), making FDG PET/CT a feasible study method (Barrington et al. 2014). The high uptake of FDG in CHL has been proposed to be caused by the interaction between HRS cells and the microenvironment cells (via cytokine production), where HRS cells reprogram the metabolism of microenvironment cells. This theory is supported by the "on-off" phenomenon seen in HL, where during chemotherapy the cytokine production and glycolytic activity of HRS cells is quickly shut down, and this can be seen as negative PET/CT. In cases of chemo-resistant HL, HRS cells continue their interaction with microenvironment cells, and hence FDG-PET/CT remains positive. (Zaucha et al. 2019) FDG accumulation differs between CHL subtypes and is presented in Table 14 (Baba et al. 2011). In NLPHL, the role of FDG-PET/CT is not that well established, as the FDG avidity is lower than in CHL (Xing & Savage 2013).

Table 14. CHL subtype and FDG accumulation. (Modified from Baba et al. 2011)

Subtype	FDG accumulation
Nodular sclerosis	High
Mixed cellularity	Moderate to high
Lymphocyte-rich	Low
Lymphocyte-depleted	Moderate to high

FDG-PET/CT has a well-defined role in the management of CHL (Barrington & Mikhaeel 2014; Hutchings et al. 2006; Zaucha et al. 2019):

1. Baseline study for staging HL, guiding the correct treatment choice.
2. Interim-PET/CT is performed after two cycles of chemotherapy, where the treatment can be adjusted according to response analysis.
3. End-of-treatment PET/CT (4–6 weeks after completion of chemotherapy and minimum of 12 weeks after radiotheraphy), where treatment response is evaluated.

As in NHLs, the Deauville score (Table 8) is used to visually assess the tumor's metabolic activity at interim and end-of-treatment FDG PET/CT (Zaucha et al. 2019). The negative prognostic value of FDG-PET/CT is excellent in HLs, but the positive predictive value of interim FDG-PET/CT varies, and hence a biopsy is recommended to confirm such results (Baba et al. 2011). Semi-quantitative methods based on SUVs (Zaucha et al. 2019) and tissue biomarkers can also here be useful in improving the analysis of FDG-PET/CT (Agostinelli et al. 2016).

2.3.3.4 Pitfalls

Although CHL and NLPHL have a rather unique histology and immunophenotype, there are several pitfalls in their diagnostics:

- Grey zone lymphomas. Includes intermediate features of CHL and DLBCL. (Wang et al. 2019)
- Composite lymphomas. HL and NHL can present simultaneously in the same patient and can even be clonally related. (Küppers et al. 2014)
- EBV-positive DLBCL, NOS. This DLBCL subtype has overlapping histological features with CHL and/or THRLBCL. (Nicolae et al. 2015)
- EBV-associated B-cell lymphoproliferations. Including polymorphic lymphoproliferative disorders, EBV+ mucocutaneous ulcers and infectious mononucleosis-like hyperplasia. All need to be noticed in the differential diagnosis of CHL as they may mimic CHL. (Natkunam et al. 2017)
- ALK+ anaplastic large cell lymphoma. Although it is a T-cell lymphoma, it may in some cases mimic nodular sclerosis CHL. (Vassallo et al. 2006)
- Peripheral T-cell lymphomas. Can contain HRS-like B-cells that express CD15 and CD30 and are EBV-positive, and hence be misdiagnosed as CHL. (Moroch et al. 2012)
- Differential diagnosis of NLPHL. The rarity of NLPHL can cause misdiagnosis, i.e., as lymphocyte-rich CHL, NHL, reactive lesions (Xing & Savage 2013), THRBCL, or progressive transformation of germinal centers. (Goel et al. 2014)
- False-positive findings on FDG PET/CT. Including infection, inflammation, reactive changes after treatment (i.e., pulmonary drug toxicity after bleomycin, increased activity after radiation therapy or granulocyte colony-stimulating factor therapy). A biopsy is preferred if a relapse is suspected on FDG PET/CT. (Kazama et al. 2005; Townsend & Linch 2012)

2.3.4 Staging, prognosis and treatment

All CHLs are treated with first-line combination therapy, which includes chemotherapy and radiation therapy. The treatment choices for HLs are presented in Table 15, respectively (Bröckelmann & Engert 2015; Eichenauer et al. 2018; Kaloyannidis et al. 2020; Shah & Moskowitz 2018; Younes et al. 2016).

The intensity of the treatment is selected by defining the risk of aggressive disease with the Ann Arbor staging system (Table 9) and risk stratification. Risk stratification method used in early stage HL has some variations between study groups and is performed in Finland according to the German Hodgkin Study Group (GHSG) (Townsend & Linch 2012). In advanced-stage HL, the International Prognostic Score (IPS) is still widely used (Moccia et al. 2012) although it is based on HL patients treated prior to 1990 (Hasenclever & Diehl 1998). A simplified version of IPS which includes only age > 45, Hemoglobin < 105 and stage IV ("IPS-3") has been shown to have similar results compared to the original IPS (Hayden et al. 2020). These risk stratification methods are presented in Table 16.

Table 15. Treatment of classic Hodgkin lymphoma.

Treatment	Indication
AVBD (2–6 cycles) + IF-RT	All stages
BEACOPP + IF-RT	Younger patients with poor response
Autologous or allogeneic stem cell transplantation	Relapsed or refractory CHL
Antibody-drug conjugate (Brentuximab Vedotin)	Relapsed or refractory CHL
Immune checkpoint inhibitor antibody for PD-L1/2 (Nivolumab)	Relapsed or refractory CHL

AVBD= doxorubicin, bleomycin, vinblastine, dacarbazine
IF-RT=involved-field radiation therapy
BEACOPP= bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
PD-L1/2=programmed death ligands 1 and 2

Table 16. Risk stratification in early stage Hodgkin lymphoma by GHSG and in advanced stage Hodgkin Lymphoma by International Prognostic Score. (Modified from Townsend et al. 2014)

Early (ST I-IIA)	Advanced (ST IIB-IV)
Large mediastinal tumor (> 1/3 of thoracic width)	Age ≥ 45
Extranodal organs affected	Male gender
Three or more affected lymph node areas	Hemoglobin level < 105 g/l
ESR* >30 mm/h + B-symptoms (ST IB disease) **or** ESR* > 50 mm/h when B-symptoms are not present (ST IA, IIA disease)	Albumin level < 40 g/l
	WBC** ≥ $15x10^9$/l
	Lymphocyte count < 0.6 $x10^9$/l or < 8%
	Stage IV disease

Early favourable: ST I-IIA, no risk factors
Early unfavourable: ST I-IIA with risk factors
Advanced favourable: ST IIB-IV with 0–3 risk factors (5-year PFS 60–80%)
Advanced unfavourable: ST IIB-IV with >3 risk factors (5-year PFS 40–50%)
* ESR=erythrocyte sedimentation rate
**WBC=white blood cell count

Limited stage (STI-II) NLPHL is commonly treated by surgically removing the affected lymph node (as a diagnostic procedure), observation, or radiation, whereas NLPHL in advanced stages is treated as CHL/DLBCL with rituximab-containing regimens, preferably R-CHOP. (Bartlett 2020; Eichenauer et al. 2018; Spinner et al. 2018)

2.4 Somatostatin receptors

Somatostatin is a peptide hormone that inhibits various cellular functions both in normal and tumor cells, including hormone secretion, cell proliferation, and angiogenesis. The antiproliferative effects can be direct mechanisms such as inhibition of growth factor receptor signaling, induction of apoptosis and cell cycle arrest, or indirect mechanisms such as inhibition of angiogenesis, inhibition of cytokine release, and downregulation and inhibition of growth factors. (Benali et al. 2000; Theodoropoulou & Stalla 2013)

The actions of somatostatin are mediated via five different somatostatin receptors (SSTR1-5) belonging to the G-protein coupled transmembrane receptor family. SSTR subtype 2 has two further protein isoforms, SSTR2a and SSTR2b. (Benali et al. 2000) SSTRs are expressed in a wide variety of normal tissues and solid tumors, with SSTR2 being the predominant subtype in the majority of tumors (Reubi et al. 2001). Among solid tumors, neuroendocrine tumors (NETs) have especially high SSTR expression, and the expression is connected to better prognosis (Brunner et al. 2017; Graf et al. 2019) and tumor differentiation (Theodoropoulou & Stalla 2013).

2.4.1 SSTRs and the immune system

SSTR2-5 are found in human lymphoid cells (Benali et al. 2000). SSTRs are expressed in normal lymphoid tissues (i.e., red pulp in the spleen, medulla of the thymus, germinal centers of lymphoid follicles), lymphoid cell lines, in a small subset of hematopoietic precursor cells in bone marrow, and peripheral blood cells (except for granulocytes and red blood cells). A few precursor cells in bone marrow express SSTR2. (Ferone et al. 2004; Oomen et al. 2000; van Hagen et al. 1994) Peripheral blood T- and B-lymphocytes express SSTR3. Peripheral blood mononuclear cells start expressing SSTR2A upon activation, suggesting that SSTR expression is related to activation and/or proliferation of these cells. (Lichtenauer-Kaligis et al. 2004; van Hagen et al. 1994) According to another study, peripheral blood lymphocytes expressed SSTR2, and the expression was elevated in EBV-transformed lymphocytes and in leukemic patients' lymphocytes compared to lymphocytes extracted from healthy individuals (Tsutsumi et al. 1997).

2.4.2 SSTRs in lymphomas

In 1992, Reubi et al. showed that lymphomas expressed SSTRs by performing an autoradiography study of 31 surgically removed lymphoma tissue samples. They further demonstrated that imaging with gamma-camera scintigraphy could detect lymphoma lesions in four patients. (Reubi et al. 1992) Also their *in situ* hybridization analysis showed abundant SSTR2 expression in lymphomas (Reubi et al. 1994). Recently, SSTR2a IHC analysis has shown diffuse membrane immunoreactivity in follicular dendritic cells in 100% of FLs (Tao et al. 2019).

Several studies have shown that lymphomas can be visualized with SSTR analogue gamma-camera scintigraphy (van den Anker-Lugtenburg et al. 1996; Vanhagen et al. 1993). The most promising results were reported for Hodgkin lymphomas where SSTR scintigraphy was positive in 98–100% of patients and had high sensitivity especially in supradiaphragmatic areas (Lugtenburg et al. 2001; van den Anker-Lugtenburg et al. 1996). Also extragastric MALT lymphomas were shown to be positive on SSTR scintigraphy, suggesting that SSTR scintigraphy could be used to differentiate between extragastric and gastric MALT lymphomas and in therapy monitoring (Morgensztern et al. 2004; Raderer et al. 1999; Raderer et al. 2001). Recently, 40% of aggressive B-cell NHLs of the nasopharynx were shown to be SSTR2 positive (Chen et al. 2019). Additionally, a case of pediatric HL showed co-expression of all five SSTRs (1-5) in RT-PCR analysis (Harda et al. 2020).

Contradictory results have also been reported. In 1995, a comprehensive review article concluded that SSTR scintigraphy was not suitable for initial staging of malignant lymphomas due to poor sensitivity (Goldsmith et al. 1995) Later, SSTR scintigraphy studies with NHL patients showed 84–85 % positivity in scans but the sensitivity was low, especially in infradiaphragmatic lesions (Ivancevic et al. 1997; Lugtenburg et al. 2001; van den Anker-Lugtenburg et al. 1996). In a multi-method study with RT-PCR, autoradiography and IHC showed absent or low SSTR expression in lymphomas, and the expression was limited to SSTR2 and SSTR3 subtypes (Dalm et al. 2004). Another review concluded also that SSTR scintigraphy is not useful in diagnosing malignant lymphomas but suggested a diagnostic niche of extragastric MALT-type lymphomas where SSTR scintigraphy could be exploited in staging and restaging (Ferone et al. 2005). More recently, SSTR IHC was reported to show low receptor expression in MALT lymphomas, with SSTR5 being the most prominent receptor subtype (positive in 50% of cases) (Stollberg et al. 2016).

In the past decade, two case reports have shown that DLBCL has mimicked another cancer in SSTR-based imaging. In one study, DLBCL mimicked NET in ^{68}Ga-DOTANOC PET/CT (Jain et al. 2014). Another study described a patient case

where DLBCL mimicked meningioma on ^{68}Ga-DOTATATE PET/CT (Lapa et al. 2013).

Table 17. Most relevant studies on SSTRs in lymphomas.

Authors (year)	n=	Lymphoma subtype	Methods	Results
Chen et al. 2019	15	B-NHL	SSTR2 IHC	40% of patients were SSTR2 positive
Stollberg et al. 2016	55	MALT	SSTR and CXCR4 IHC	50% of the patients expressed SSTR5 whereas the expression of other SSTRs was low
Dalm et al. 2004	10	NHL, HL	RT-PCR, IHC, autoradiography	RT-PCR showed low expression levels of SSTR2 and SSTR3 mRNA and their IHC analysis remained negative. Autoradiography studies showed low binding affinity.
Lugtenburg et al. 2001	126	HL	SSTR scintigraphy	SSTR scintigraphy had 94% lesion-related sensitivity. Sensitivity was better in supradiaphragmatic lesions.
Raderer et al. 1999	29	MALT	SSTR scintigraphy, northern blotting	SSTR scintigraphy was positive in extragastric MALT lymphomas where large amounts of SSTR2 mRNA was detected in northern blotting.
Reubi et al. 1992	31	NHL, HL	In-vitro SSTR autoradiography	SSTR autoradiography was positive in most lymphoma samples

B-NHL=B-cell non-Hodgkin lymphoma
MALT=extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
NHL=non-Hodgkin lymphoma
HL=Hodgkin lymphoma
IHC=immunohistochemistry
RT-PCR=reverse transcription polymerase chain reaction

2.4.3 SSTR-based PET/CT imaging

SSTR-expressing tumors can be visualized with gamma-camera scintigraphy or PET/CT by using radiolabeled somatostatin analogues (Table 18). For example, ^{68}Ga-DOTA-conjugated-peptide PET/CT is routinely used in NETs for diagnosing, staging, re-staging, evaluating prognosis, selecting treatment, and monitoring treatment response. (Bozkurt et al. 2017)

Table 18. SSTR expressing tumors that may be visualized with ^{68}Ga-DOTA-conjugated-peptide PET/CT (Modified from Bozkurt et al. 2017).

High expression	Low or varying expression
Gastro-entero-pancreatic neuroendocrine tumors	Breast carcinoma
Neuroendocrine tumors of the lungs	Prostate carcinoma
Sympatho-adrenal system tumors	Lymphomas
Meningioma	Melanoma
	Non-small-cell lung cancer
	Sarcoma
	Renal cell carcinoma
	Differentiated thyroid carcinoma
	Astrocytoma
	Head and neck cancer

Somatostatin analogues specific only to SSTR2 were mainly used in the earliest scintigraphy studies. Nowadays, DOTA-conjugated peptides with improved affinity profiles are predominantly used (Ambrosini et al. 2011), although also SSTR-antagonists have recently been suggested for imaging (Fani et al. 2017). The most commonly used ^{68}Ga-labelled DOTA-conjugated peptides are listed below:

- [68Ga-DOTA0,Tyr3]octreotate (68Ga-DOTATATE) with very high affinity to SSTR2.
- [68Ga-DOTA0 -Tyr3]octreotide (68Ga-DOTATOC) with high affinity to SSTR2 and 5.
- [68Ga-DOTA0-1NaI3]octreotide (68Ga-DOTANOC) with high affinity to SSTR2, 3 and 5.

As PET/CT has replaced scintigraphy as an imaging modality in the recent years, the resolution of acquired images has improved significantly (Virgolini et al. 2010). 68Ga-DOTA-conjugated-peptide PET/CT images can be interpreted by using semiquantitative analysis based on SUVs and by visual analysis with the Krenning scoring system (Table 19) (Hofman et al. 2015).

Table 19. Krenning scoring system for visual grading of pathologic uptake in ^{68}Ga-DOTATATE PET/CT (modified from Hofman et al. 2015).

Score	Intensity
0	No uptake
1	Very low uptake
2	Uptake ≤ liver
3	Uptake > liver
4	Uptake > spleen

It must be noticed that tracer uptake is not specific to malignant tumors but rather presents increased expression of SSTRs. The main pitfalls of ^{68}Ga-DOTA-conjugated-peptide PET/CT are listed below (Ambrosini & Fanti 2014; Hofman et al. 2015; Ivanidze et al. 2019):

- Physiologic uptake in organs. Pancreas, liver, adrenal glands, spleen, thyroid, stomach.
- False-positive findings. Accessory spleen, head of pancreas, osteoblastic activity (i.e., fracture or degenerative bone disease), contamination of clothes/skin with urine, inflammation, and incidental findings (i.e., meningioma, lymphoma).
- False-negative findings. High grade and poorly differentiated NETs that have lost their SSTR expression. Previous chemotherapy and octreotide treatment/endogenous production of somatostatin can modify SSTR expression in tissues.

2.4.4 SSTR-based treatment

SSTRs can be used as targets for cancer treatment, but it has been suggested that the target tumor needs to have high SSTR expression for an adequate therapeutic response (Kong & Hicks 2019). Long-acting somatostatin analogues injected subcutaneously ("cold octreotide") and SSTR-targeted PRRT with yttrium 90 (^{90}Y)- or lutetium 177 (^{177}Lu) DOTATE or DOTATOC ("hot octreotide") have been used successfully in treating multiple conditions including NETs, acromegaly, TSH-secreting pituitary adenomas, and carcinoid syndrome (Lamberts et al. 1996; Theodoropoulou & Stalla 2013). PRRT is based on bringing β- or γ-emitters (^{90}Y or ^{177}Lu) in contact with malignant cells using direct receptor binding when the emission destroys malignant cells. ^{177}Lu has a more favourable side-effect profile compared to ^{90}Y, which is why it is the currently preferred radioligand in clinical practice. PRRT is considered as a safe treatment method with minimal adverse effects, particularly on the kidneys. (Ivanidze et al. 2019; Kong & Hicks 2019)

2.4.5 Theranostic approaches to lymphomas

As SSTRs can be used in both diagnostic and treatment methods, they offer a theranostic (diagnostic and therapeutic) approach to the management of SSTR-expressing tumors. Some theranostic agents are already used for lymphomas:

- A theranostic agent targeting CD20 antigen (^{111}In- or ^{90}Y-ibritumomab) has been used in diagnostic scans and in radioimmunotherapy of NHLs. (Ballinger 2018; Ivanidze et al. 2019).
- A review article by Eskian et al. (2018) concluded that adding radioimmunotherapy to the conditioning regimen prior to allogenous stem cell transplantation improves survival compared to BEAM alone in NHLs (Eskian et al. 2018).

Lymphomas are highly radiosensitive (Chan et al. 2011), which raises the question of the possibility to exploit SSTR-targeted PRRT also in lymphomas regardless of the lower SSTR densities. Another possibility could be to use SSTR-targeted PRRT in personalized medicine in cases where abundant SSTR expression is found in a random lymphoma patient.

2.5 Chemokine receptor CXCR4

Chemokine receptor CXCR4 and its ligand stromal cell-derived factor-1 (SDF-1 or CXCL12) regulate many biological processes including cardiac and neuronal development, stem cell motility, neovascularization, and tumorigenesis. CXCR4 is expressed at the cell surface of many normal and malignant immune system cells including neutrophils, monocytes, T- and B-cells, B-cell precursors, macrophages, immature and mature thymic T-cells, and CD34+ progenitor cells in blood and bone marrow. In normal tissues, CXCR4/CXCL12 axis is essential for B-cell development, retention of B-cell precursors in bone marrow, and homing B-cells to lymph nodes. In malignant tissues, CXCR4/CXCL12 axis is associated with angiogenesis, migration of tumor cells to metastatic sites, and higher aggressiveness. (Moreno et al. 2015; Peled et al. 2018; Vandercappellen et al. 2008)

2.5.1 CXCR4 in lymphomas

Several previous studies have investigated the role of CXCR4 in lymphomas and are presented in Table 20.

Table 20. Most relevant studies of CXCR4 in lymphomas.

Authors (year)	n=	Lymphoma subtype	Methods	Results
Laursen et al. (2019)	414	DLBCL	CXCR4 mRNA expression analysis	High CXCR4 expression was significantly associated with poor outcome for R-CHOP-treated patients but not for CHOP treated.
Haug et al. (2019)	36	MALT	^{68}Ga-Pentixafor PET/MRI	33/36 of patients had increased uptake in ^{68}Ga-Pentixafor PET/MRI.
Chen et al. (2015)	743	DLBCL	CXCR4 IHC	28.8% of the patients were CXCR4 positive. CXCR4 expression was associated with poorer OS and PFS, male gender, bulky tumor, high Ki-67, ABC subtype, and Myc, Bcl-2, or p53 overexpression.
Stollberg et al. (2016)	55	MALT	CXCR4 and SSTR IHC	CXCR4 expression was detected in 92% of patients. There was a correlation with CXCR4 expression and Ki-67 in gastric MALT lymphomas.
Moreno et al. (2014)	94	DLBCL	CXCR4 IHC	CXCR4 expression was connected to recurrent disease and decreased PFS and OS in 50% of patients.
Menter et al. (2014)	45	Primary testicular DLBCL	CXCR4 IHC	CXCR4 IHC was positive in 52% of patients and high expression was connected to poorer PFS.

DLBCL=diffuse large B-cell lymphoma
MALT=extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
R-CHOP=rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone
IHC=immunohistochemistry
PFS=progression-free survival
OS=overall survival
ABC=activated B-cell-like

2.5.1.1 Localization of CXCR4 in lymphoma cells

CXCR4 expression was localized to the nucleus or cytoplasm in primary CNS lymphomas (Jahnke et al. 2005; Lemma et al. 2016), whereas membranous CXCR4 expression was detected in DLBCL cell lines which had higher dissemination and aggressive behavior (Moreno et al. 2015). CXCR4 internalization from the cell membrane was detected in DLBCL cells that homed to the CNS, bone marrow or lymph nodes (and hence were exposed to chemokine CXCL12), causing a dot-like staining in CXCR4 IHC. Treatment with a CXCR4 antagonist caused CXCR4 internalization in DLBCL cell lines and prevented their dissemination and migration towards CXCL12 expressing tissues, especially lymph nodes (Moreno et al. 2015). In MALT lymphoma, distinct membranous CXCR4 staining was detected in germinal centers of follicles, whereas surrounding tumor cells presented with a strong intracellular dot-like staining pointing to receptor internalization (Stollberg et al. 2016).

2.5.1.2 CXCR4 expression in DLBCL

Three studies have shown that CXCR4 upregulation is connected to tumor cell dissemination, disease progression, and poor survival in patients with DLBCL (Chen et al. 2015; Menter et al. 2014; Moreno et al. 2015). Furthermore, CXCR4 expression in DLBCL was associated with male gender, bulky tumor, ABC subtype, high Ki-67 index, and overexpression of Myc, Bcl-2, or p53 (Chen et al. 2015). Another study with rituximab treated DLBCL patients showed CXCR4 expression in 60.7% of patients and the expression was associated with high serum LDH level, high IPI score, and non-GCB subtype (Xu et al. 2018).

2.5.1.3 CXCR4 expression in MALT lymphomas

In one study, CXCR4 IHC was found to be highly positive in 92% of patients, and there was a correlation with CXCR4 expression and Ki-67 in gastric tumors (Stollberg et al. 2016). Another study showed that CXCR4 expression was lost during malignant transformation from H. pylori-associated gastritis to MALT lymphoma. The same study also reported that CXCR4 expression was noticed in nodal marginal B-cell lymphomas and nodal DLBCLs, but not in extranodal (i.e., gastric) manifestations of these lymphomas. (Deutsch et al. 2013)

2.5.1.4 CXCR4 expression in MCL

In one study, human MCL cells and MCL cell lines had high CXCR4 expression, and the CXCR4-antagonist Plerixafor was able to inhibit adhesive interactions between MCL cells and marrow stromal cells (Kurtova et al. 2009). Another study showed that experimental CXCR4 silencing in human MCL cell lines decreased cell proliferation and adhesion to bone marrow stromal cells significantly. They also showed that CXCR4 expression was upregulated in chemotherapy resistant MCL cells, leading to enhanced lymphoma cell survival. (Chen et al. 2016) Recently, SOX11 was shown to directly upregulate the expression of CXCR4 in MCL, activating certain pathways that increase homing and invasion of MCL cells and also cell adhesion-mediated drug resistance, leading to more aggressive disease (Balsas et al. 2017).

2.5.1.5 CXCR4 and prognosis

Four studies have reported that CXCR4 could be used as a prognostic marker in NHLs. One study with 94 DLBCL patients showed that CXCR4 expression was an independent predictor of worse PFS in GCB-like DLBCL (Moreno et al. 2015). High CXCR4 expression was connected to poor prognosis in R-CHOP treated DLBCL

patients due to CXCR4 impairing the rituximab-induced response (Laursen et al. 2019). In NHL patients, decreased CXCR4 expression in bone marrow after treatment was connected to better prognosis (Mazur et al. 2014). In primary testicular DLBCL, high expression of CXCR4 was connected to poorer PFS ($p < 0.003$) (Menter et al. 2014).

2.5.2 CXCR4-based imaging

Two studies have shown that extranodal marginal zone lymphomas can be visualized with a CXCR4-targeted radiolabeled tracer, ^{68}Ga-Pentixafor, on PET/MRI (Haug et al. 2019; Herhaus et al. 2017). A recent study showed that ^{68}Ga-Pentixafor PET was positive in 10/11 CNS lymphomas and tracer uptake correlated with treatment response (Herhaus et al. 2020). Another recently published study with 27 newly diagnosed NHLs showed that DLBCLs, FLs, MCL, unclassified B-cell lymphomas, marginal zone lymphomas, and enteropathy-associated T-cell lymphomas were positive on ^{68}Ga-Pentixafor PET, whereas PTCL NOS and NK/T-cell lymphomas were not. They also demonstrated that the uptake of ^{68}Ga-Pentixafor was higher than ^{18}F-FDG in marginal zone lymphomas. (Pan et al. 2020)

2.5.3 CXCR4-based treatment

Three studies with human DLBCL cell lines have shown *in vivo* and *in vitro* that CXCR4 antagonists enhance the effects of rituximab and inhibits dissemination and disease progression (Beider et al. 2013; Hu et al. 2012; Reinholdt et al. 2016). A human anti-CXCR4 antibody even had antitumor activity as was shown in NHL xenograft models (Kuhne et al. 2013). In another study, treatment with CXCR4-targeting antagonists called pepducins increased survival in disseminated lymphoma xenograft-bearing mice and increased the apoptotic effect of rituximab (O'Callaghan et al. 2012).

In NHLs and HLs, the CXCR4 antagonist Plerixafor has already been used in combination with granulocyte-colony stimulating factor for mobilization of hematopoietic stem cells prior to autologous stem cell transplantation, where it has helped to collect enough stem cells in poor mobilizers (Yang et al. 2019; Yuan et al. 2017).

Also, radioligand therapy targeting CXCR4 was shown to be a feasible method in refractory/relapsed DLBCL as a part of the conditioning regimen before allogeneic stem cell transplantation (Lapa et al. 2019).

3 Aims

The aim of our study was to determine whether lymphomas express SSTRs sufficiently to be visualized as tracer-positive on ^{68}Ga-DOTANOC PET/CT and hence create a potential pitfall in the differential diagnostics of NETs. We then wanted to further evaluate SSTR and CXCR4 status from the tissue samples of six different lymphoma subtypes to determine whether some lymphoma subtypes could be potential targets for developing SSTR/CXCR4-based diagnostic methods or treatments. Lymphomas are a highly heterogeneous disease entity with several potential pitfalls in their diagnosis, and new molecular markers are needed to develop new prognostic, diagnostic and treatment methods. Additionally, an epidemiological study on the incidence and mortality of HL subtypes in Finland during 1996–2015 was undertaken to understand more about the heterogeneic clinical behavior of HLs. The specific study aims were:

I. To analyze SSTR 2, 3 and 5 expressions immunohistochemically in tissue samples from newly diagnosed lymphoma patients, and to match these results to corresponding ^{68}Ga-DOTANOC PET/CT images to evaluate whether lymphomas express SSTRs enough to be visualized as positive on ^{68}Ga-DOTANOC PET/CT, hence creating a potential pitfall when diagnosing NETs.

II. To investigate the expression profile of SSTR2, 3, and 5 and CXCR4 in six lymphoma subtypes (DLBCL, FL, MCL, MALT, PTCL, and HL) and hence explore the possibility to use them as molecular targets in developing new diagnostic or therapeutic methods.

III. To investigate the incidence and mortality of CHL subtypes and NLHPL in Finland in 1996–2015 by gender and age to discover the current trends over the last two decades.

4 Materials and Methods

4.1 Study I

4.1.1 Study design

In this prospective pilot study, SSTR2, 3, and 5 statuses were evaluated immunohistochemically and by ^{68}Ga-DOTANOC PET/CT imaging from 21 patients with newly diagnosed lymphoma (Figure 1). FDG PET/CT was used as a reference standard. Both of the PET/CT images were performed prior to any treatment in random order, except for patient No. 16 who developed disruptive itching as a B-symptom after ^{68}Ga-DOTANOC-PET/CT imaging and hence received prednisone for 3 days before ^{18}F-FDG PET/CT. SSTR2, 3 and 5 immunohistochemistry (IHC) was performed on the patients' tissue samples obtained from routine biopsies. The patients were recruited during 2014–2015 from the area of the Hospital District of Southwest Finland. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland and by Turku Clinical Research Centre (ClinicalTrials.gov identification number NCT02389101). Informed consent was obtained from all patients upon recruitment.

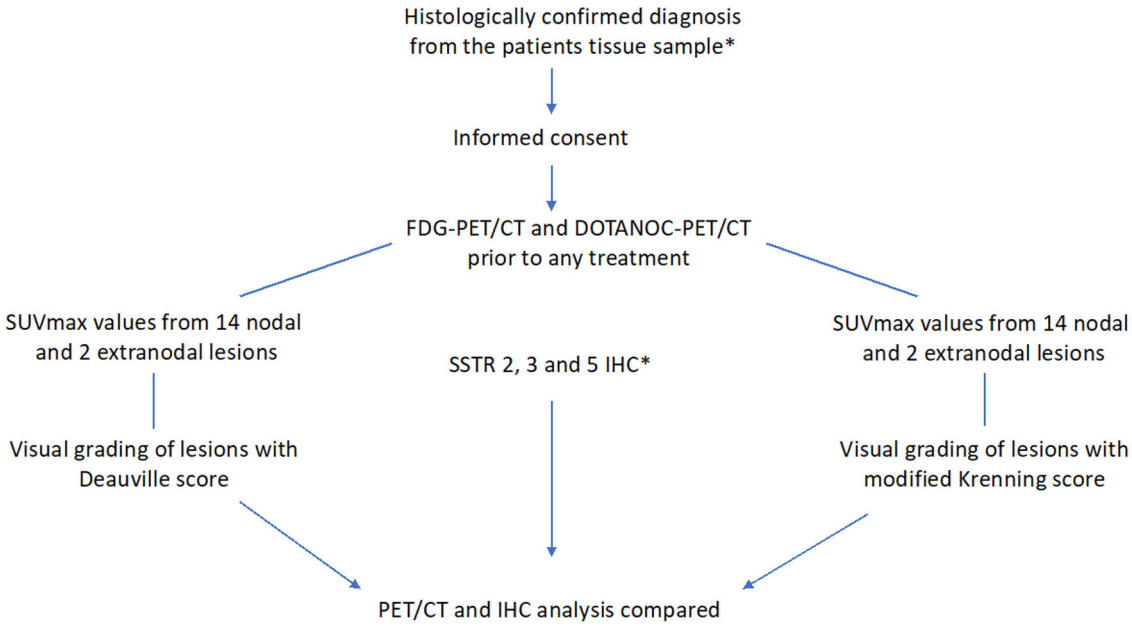

Figure 1. Sequence of events in Study I. *Same tissue samples were used.

4.1.2 Patient characteristics

A total of 21 patients with newly diagnosed lymphoma were enrolled in the study, including 11 males and 10 females with a median age of 66 years. Inclusion criteria were age over 18 years, histologically confirmed lymphoma diagnosis, and no lymphoma treatments given prior to participation. Exclusion criteria were age under 18 years, pregnancy or lactation, any significant disease (i.e., renal failure), or any other medical or psychiatric condition that could compromise the patient's ability to participate in the study. The patients presented a mix of lymphoma subtypes, since specific subtypes were not a required in this pilot study. Patient characteristics are presented in Table 21. Some of the patients were further recruited to Study II.

Table 21. Patient characteristics in Study I.

ID	Sex (M/F)	Age	Lymphoma subtype	Stage	Biopsy type	Biopsy location	FDG-PET/CT	DOTANOC-PET/CT	SSTR2	SSTR3	SSTR5	In study II
1	M	68	DLBCL (GBC)	IVB	Surgical	E	x	x			UC	x
2	M	61	DLBCL (T-cell rich)	IVB	Surgical	LN	x	x				x
3	F	63	DLBCL (GBC)	IVA	Surgical	LN	x	x	x			x
4	M	66	DLBCL (ABC)	IVA	Surgical	E	x	x				x
5	F	72	DLBCL (GBC)	IIA	Core	E	x	x				
6	F	62	FL gradus 3A	IVA	Surgical	LN	x	x	x			x
7	F	74	FL gradus 3A	IIIA	Surgical	LN	x	x	x			x
8	F	70	FL gradus 1-2	IIIA	Surgical	LN	x		x			x
9	M	66	FL gradus 1-2	IIIA	Surgical	LN	x		x			
10	M	61	MCL	IVB	Surgical	E	x					
11	M	73	MCL	IVA	Core	E	x	x				
12	F	82	SLL	IVA	Surgical	LN	x	x			x	
13	F	76	SLL	IIIA	Surgical	LN	x					
14	F	73	SLL	IIIA	Core	LN						
15	F	59	MALT	IIA	Surgical	E	x					x
16	M	66	Anaplastic large cell lymphoma, ALK-	IIIB	Surgical	LN	x	x				
17	F	65	Nodular sclerosis CHL	IVB	Surgical	LN	x	x	x	x		x
18	M	67	Mixed cellularity CHL	IVA	Surgical	E	x		x	x		x
19	M	78	Nodular sclerosis CHL	IIIA	Surgical	LN	x	x	UC	x	UC	x
20	M	40	Nodular sclerosis CHL	IIB	Surgical	LN	x	x	x	x	x	
21	M	63	NLPHL	IIA	Surgical	LN	x		x			x

LN=lymph node. E=extranodal lesion. UC=uncertain. X refers to a positive result at PET/CT and IHC, and an empty slot to negative.

4.1.3 PET/CT imaging and imaging analysis

The imaging protocol for both PET studies was in accordance with the European Association of Nuclear Medicine (EANM) guidelines and covered the whole body from mid-thigh to the base of the skull. The mean injected activity of ^{68}Ga-DOTANOC was 126 MBq (range 109–143) and that of ^{18}F-FDG 297 MBq (range 218–411), respectively. The start of acquisition was 60 min after injection in all cases. The acquisition time was 4 minutes per bed position at ^{68}Ga-DOTANOC PET/CT and 2 or 3 minutes per bed position at ^{18}F-FDG PET/CT depending on the scanner used. The two scanners used were 64-row Discovery STE and VCT (General Electric Medical Systems, Milwaukee, WI, USA). Low-dose CT was used for attenuation correction. PET images were reconstructed in 3D mode and 128 × 128 matrix size using an ML-OSEM reconstruction algorithm. An ADW 4.6 workstation (General Electric Medical Systems, Milwaukee, WI, USA) was used for evaluating the images.

Two nuclear medicine specialists evaluated the images and were blinded to the SSTR IHC results. Maximum standardized uptake values (SUVmax) were determined from 14 lymph node and two extranodal regions with the highest uptake

in each patient. The SUVmax values were corrected for body weight and injected dose. Lesions were then graded with the Deauville score (1–5) on FDG PET/CT (Barrington et al. 2014) and modified Krenning score (0–4) on ^{68}Ga-DOTANOC PET/CT (Hofman et al. 2015). Lymphomas were graded as FDG-positive if the Deauville score was ≥ 3 and DOTANOC-positive if the modified Krenning score was ≥ 2. To adjust the Krenning score to meet the purposes of scoring lymphomas, we included also lesions with uptake clearly higher than surrounding tissues as ^{68}Ga-DOTANOC-positive lesions ("modified Krenning score").

4.1.4 Immunohistochemical analysis

SSTR2, 3, and 5 expression was analyzed immunohistochemically (SSTR IHC) from the patients' tissue samples obtained from routine biopsies. A pathologist specialized in lymphomas evaluated SSTR IHC results blinded to the DOTANOC PET/CT findings. SSTR expression was reported as positive (=tracer uptake in malignant cells) or negative. Also, a descriptive analysis was given to point out whether there was SSTR positivity in malignant or other (non-neoplastic) cells possibly contributing to positive ^{68}Ga-DOTANOC PET/CT scans.

Formalin-fixed paraffin-embedded tumor tissues were sectioned at 3 μm. Primary antibodies used for IHC were SSTR2/UMB1 (dilution 1:1000), SSTR3/UMB5 (dilution 1:2000), and SSTR5/UMB4 (dilution 1:500) (Abcam, Cambridge, UK). Staining was done with either Ventana Benchmark XT Autostainer (UMB1-staining) with ultraVIEW Universal Detection Kit (Ventana, Strasbourg, France), or Labvision Autostainer with Envision secondary antibody (Dako, Glostrup, Denmark).

4.1.5 Metabolite analysis

Analysis of unchanged [68Ga]-DOTANOC and its radioactive metabolites in the plasma of six patients was carried out with radio-high-performance liquid chromatography (radio-HPLC). Venous blood samples were collected at 15, 45, and 90 min after intravenous injection of [68Ga]-DOTANOC and processed for radio-HPLC analysis with a Luna C18 (2) column (5 μm, 100 Å, 250 × 10 mm, Phenomenex, USA). A gradient with water (A) and acetonitrile (B), both containing 0.1% trifluoroacetic acid (TFA), was used as follows: 100% A at 0–8 min and 10–12 min, 30% A and 70% B at 8–9 min, at a flow rate of 5.0 ml/min.

4.2 Study II

4.2.1 Study design

Study II was a continuation to Study I. In this retrospective study, SSTR2, 3, and 5 IHC and in addition CXCR4 IHC was performed on tissue samples from 103 lymphoma patients obtained from routine biopsies. Six lymphoma subtypes of special interest were selected: DLBCL, FL, MCL, HL, MALT and PTCL(/ALCL). All patients included in this study were diagnosed in the Southwest Hospital district of Finland in 2010–2019, except for three HL patients whose tissue samples analyzed in this study were taken upon relapse. Tissue samples were obtained from the local university-based Biobank (Auria Biobank) based on informed consent given by each patient. No additional biopsies were performed in this study. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland, Auria Biobank, and the Turku Clinical Research Centre.

4.2.2 Patient characteristics

A total of 103 lymphoma patients were included in this study, resulting in 24 DLBCL, 22 FL, 20 MCL, 9 MALT, 10 PTCL(/ALCL), and 18 HL cases, respectively (Table 22). Fifty-five percent of the patients were males (n=57) and 45% females (n=46) with a mean age of 63 years (range 20–86). Eighty-eight of the analyzed tissue samples were diagnostic, 12 were taken upon relapse/progression, and three were obtained at a transformed stage (HL patient Nos. 51, 58 and 61). Tissue samples were mostly excisional lymph nodes (n=65, 63%) but also bone marrow trephines (n=7, 7%) and biopsies from extranodal tissues (i.e. gastrointestinal tract, salivary glands, spleen) (n=31, 30%) were analyzed. Unfortunately, one patient's (No. 47) SSTR3 and CXCR4 stainings went missing and could not be used in this study.

Table 22. Patients characteristics in study II.

	N	%
PATIENTS	103	
MALES	57	55
FEMALES	46	45
MEAN AGE -RANGE -SD	63 20–86 13.27	
STAGE -I–II -III–IV	 28 75	 27 73
DLBCL	24	23
FL	22	21
MCL	20	19
MALT	9	9
PTCL	10	10
HL	18	18

4.2.3 Immunohistochemical analysis

Commercially available rabbit monoclonal antibodies (Abcam, Cambridge, UK) were used in SSTR2, 3 and 5 and CXCR4 immunohistochemical stainings (Table 23). First, formalin-fixed paraffin-embedded tumor tissues were sectioned at 3 µm. Staining was done with Labvision Autostainer 480S. Orion 2 steps detection system goat anti ms/rb HRP WellMed T100HRP was used as a secondary antibody.

Table 23. Antibodies used in immunohistochemical stainings.

Antibody	Type	Clone	Supplier	Dilution
SSTR2	Rabbit monoclonal	UMB1	Abcam	1:500
SSTR3	Rabbit monoclonal	UMB5	Abcam	1:500
SSTR5	Rabbit monoclonal	UMB4	Abcam	1:50, 1:500
CXCR4	Rabbit monoclonal	UMB2	Abcam	1:500

An experienced lymphoma pathologist analyzed IHC results visually by intensity of staining in the malignant cells (Table 24, Figure 2) and the proportion of the positively stained tumor cells was determined (0–100%). Next, a four-point scale was developed to describe immunopositivity (Table 25). The immunoreactive score (IRS) developed by Remmele et Steigner (1987) (Remmele & Stegner, 1987) for IHC analysis in breast cancer was not used directly but as a motivation for our own scoring system. Many of the existing IHC scoring schemes interprets mild intensity staining as negative. In highly radiation sensitive lymphomas, even a small positivity in tumor cells could be sufficient to develop new personalized treatment methods with PRRT targeting these receptors, which led us to develop our own four-point scale.

Table 24. Intensity scale used in evaluating immunohistochemical stainings.

Intensity	Definition
0	No staining
1	Mild staining
2	Moderate staining
3	Strong staining

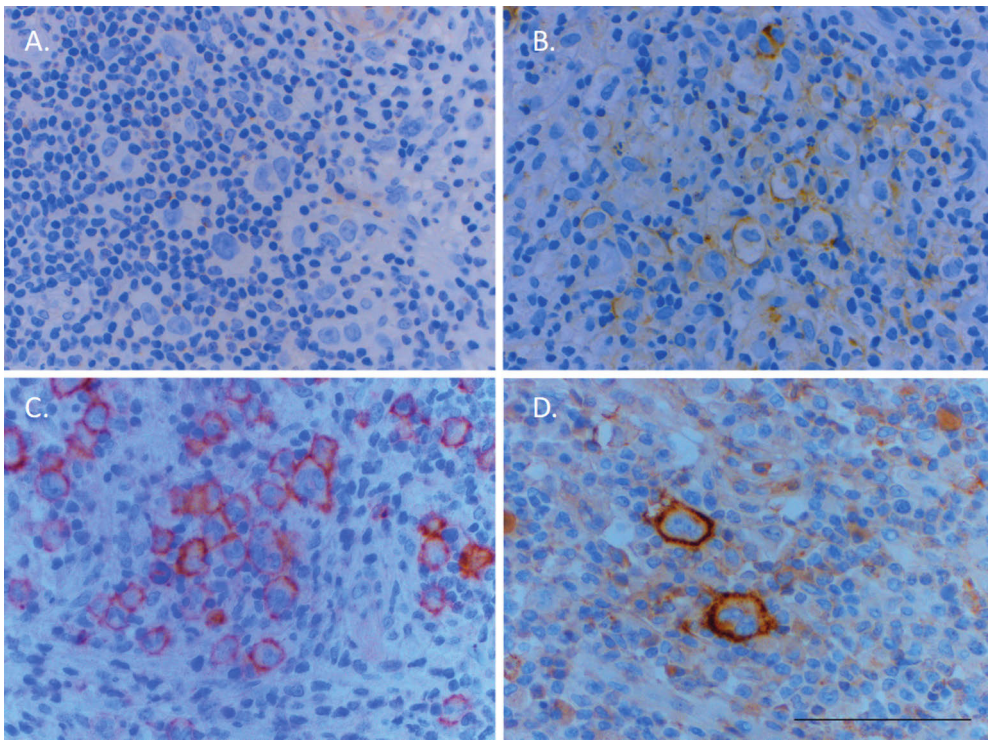

Figure 2. Examples of staining intensity in the cell membrane of malignant Reed-Sternberg/Hodgkin cells. Brown color indicates positive staining. (**A**) no staining, (**B**) mild staining, (**C**) moderate staining, and (**D**) strong staining (Modified from Juntikka et al. 2021)

Table 25. Four-point scale for describing immunopositivity.

SCORE	EXPRESSION	DEFINITION
0	Negative	No staining
1	Mild	Mild staining in < 75% or moderate staining in < 25%
2	Moderate	Mild staining in > 75%, moderate staining in > 25%, or strong staining in < 25%
3	Strong	Moderate staining in > 75% or strong staining in > 25%

4.2.4 Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26. (IBM Corp., Armonk, NY). Descriptive statistics were used to present mean (range) for age and frequencies (percentages) for categorical variables.

4.3 Study III

4.3.1 Patient characteristics

A total of 2851 HL patients diagnosed in Finland during 1996–2015 were included in the study (Table 26). The median age of the patients was 37 years (range 4–94) and there was a slight male predominance (56%). 36% of all patients were over 50 years of age at diagnosis. The data was obtained and analyzed from the FCR database during 2016–2019. All HL NOS (M9650/3) cases were checked manually and re-coded to specific HL subtypes according to the ICD-O-3, if possible (Table 9). Tissue samples were not histologically re-analyzed in this study, but the re-coding was based rather on the pathology reports as well as clinical reports sent to the FCR. In unclear cases, the study group's lymphoma oncologist was consulted. In 68 unclear cases, full original pathology reports were ordered from hospital districts around Finland or from private pathology laboratories.

Table 26. Patients characteristics in study III (modified from Juntikka et al. 2020).

HL subtype	Total n (%)	Male n (%)	Female n (%)	Median age (range)	Proportion of over 60-year-old patients
Nodular sclerosis	1529 (54)	710 (46)	819 (54)	28 (6–97)	19%
Mixed cellularity	453 (16)	279 (62)	174 (38)	57 (4–94)	59%
NLPHL	374 (13)	284 (76)	90 (24)	48 (5–87)	47%
Lymphocyte-rich	252 (8,8)	171 (68)	81 (32)	48 (5–94)	45%
Lymphocyte-depleted	30 (1.1)	20 (67)	10 (33)	64 (19–89)	70%
NOS	213 (7.5)	122 (57)	91 (43)	62 (8–94)	65%
Total	**2851**	**1586 (56)**	**1265 (44)**	**37 (4–97)**	**36%**

4.3.2 Statistical analysis

Statistical analyses were all done using the statistical software R, version 3.6.0. Incidence rates were age-standardized using the WHO world standard population. Incidence and mortality rates were calculated in four 5-year calendar periods (1996–2000, 2001–2005, 2006–2010, and 2011–2015) in each HL subtypes separately and in the total population. Age- and sex-specific incidence and mortality rates were also

calculated. Five-year age strata were used in calculating the age-specific rates, and stratification to three age groups (0–14, 15–44 and 45+) was used to analyze changes in the age-specific incidence over time, respectively. The average annual percent change (APC) and the corresponding 95% confidence interval (CI) were calculated using log-linear regression analysis as well as joint-point regression, which identifies specific shifts in trends. The Davies test was used for selection of breakpoints. Differences between the groups of median age were tested using a Mann-Whitney U test.

5 Results

5.1 Patient case report

Prior to the launch of this doctoral thesis, an encouraging patient case was observed at the Hospital district of Southwest Finland. A 65-year-old female with a history of hypothyreosis was admitted to hospital with acute upper abdominal pain in June 2013. Ultrasound examination revealed a tumor in the head of pancreas. Laparotomy was performed but the pancreatic tumor was unresectable and histologic evaluation of a targeted biopsy remained indeterminate. Postoperatively, a strongly ^{68}Ga-DOTANOC positive lesion in the head of pancreas together with slightly increased serum CgA of 6.8 nmol/l and unremarkable physical condition of the patient supported diagnosis of NET. Hence, treatment with long-acting octreotide (Sandostatin LAR, Novartis) was started and the patient remained well until spring 2014 when she was again admitted to hospital with jaundice. CT and ultrasound showed biliary obstruction due to progression of the pancreatic tumor during octreotide treatment. A permanent endobiliary stent was subsequently inserted and a new ultrasound-guided biopsy was diagnostic for DLBCL. FDG PET/CT showed positive uptake in the tumor and several additional sites. The final stage was IVAE, and the patient received standard R-CHOP treatment and consolidation radiation therapy, achieving complete remission. The patient's SSTR IHC results and DOTANOC PET/CT are presented in Figure 3.

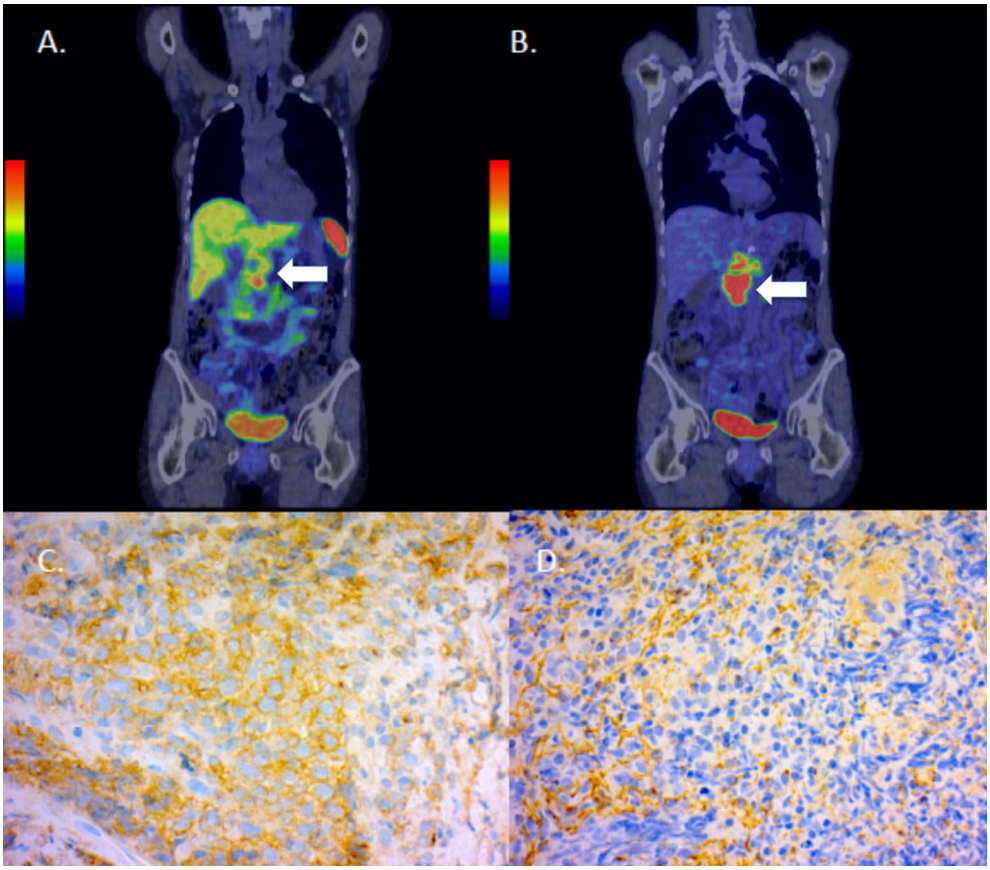

Figure 3. ^{68}Ga-DOTANOC PET/CT image (**A**) shows clear tracer uptake in the corresponding pancreatic tumor site compared to FDG PET/CT (**B**) (white arrows). SSTR2 IHC (**C**) was positive in tumor cells whereas SSTR3 IHC (**D**) remained negative, although staining in surrounding non-neoplastic cells or stroma was observed (brown). (Modified from Ruuska et al. 2018)

5.2 Some lymphomas express SSTRs which can be visualized at ^{68}Ga-DOTANOC PET/CT (Study I)

5.2.1 FDG and ^{68}Ga-DOTANOC PET/CT imaging analysis

Twenty of 21 (95%) patients had FDG-positive lymphoma upon visual analysis of PET/CT images. Correspondingly, 13 of 21 (62%) patients had ^{68}Ga-DOTANOC-positive lymphoma (Table 21). ^{68}Ga-DOTANOC positivity was seen predominantly in lymph nodes that were invariably also FDG-positive, with only one exception (patient No. 4), where four lymph nodes were ^{68}Ga-DOTANOC-positive but only two of them were FDG-positive. There was no clear correlation between SUVmax

in ^{68}Ga-DOTANOC- and FDG-positive lymph nodes (Table 27). When compared to NETs, the SUVmax values of ^{68}Ga-DOTANOC-positive lymphomas remain clearly lower.

Table 27. Comparison of the median SUVmax values at ^{68}Ga-DOTANOC PET/CT and FDG PET/CT for all 13 patients with positive findings at ^{68}Ga-DOTANOC PET/CT (modified from Ruuska et al. 2018).

Patient	Lymphoma subtype	DOTANOC SUVmax	FDG SUVmax	SSTR positivity in lymphoma/related cells likely contributed to positive ^{68}Ga-DOTANOC PET/CT
19	HL (nodular sclerosis)	9.8	8.0	**Yes**
3	DLBCL (GBC)	9.7	9.1	**Yes**
5	DLBCL (GBC)	6.1	8.8	No
17	HL (nodular sclerosis)	5.3	7.6	**Yes**
1	DLBCL (GBC)	4.6	5.9	-*
16	Anaplastic large cell	3.7	10.4	No
4	DLBCL (ABC)	3.1	4.0	No
20	HL (nodular sclerosis)	3.1	5.2	**Yes**
6	FL	2.5	7.0	**Yes**
2	DLBCL (T-cell rich)	2.3	11.5	No
11	MCL	2.3	7.6	No
7	FL	1.9	8.4	**Yes**
12	SLL	1.9	4.6	**Yes**

*not determined due to unsuccessful SSTR5 IHC.

The highest uptake of ^{68}Ga-DOTANOC was seen in a patient with nodular sclerosis CHL (No. 19) whose median SUVmax of the positive lesions was 9.8 (Figure 4). Another patient (no. 3) with DLBCL (GCB subtype) had a respective median SUVmax of 9.7 (Figure 5). This patient was the only case with conspicuous ^{68}Ga-DOTANOC-positive extranodal lesions, whereas in the majority of patients extranodal lesions were ^{68}Ga-DOTANOC-negative.

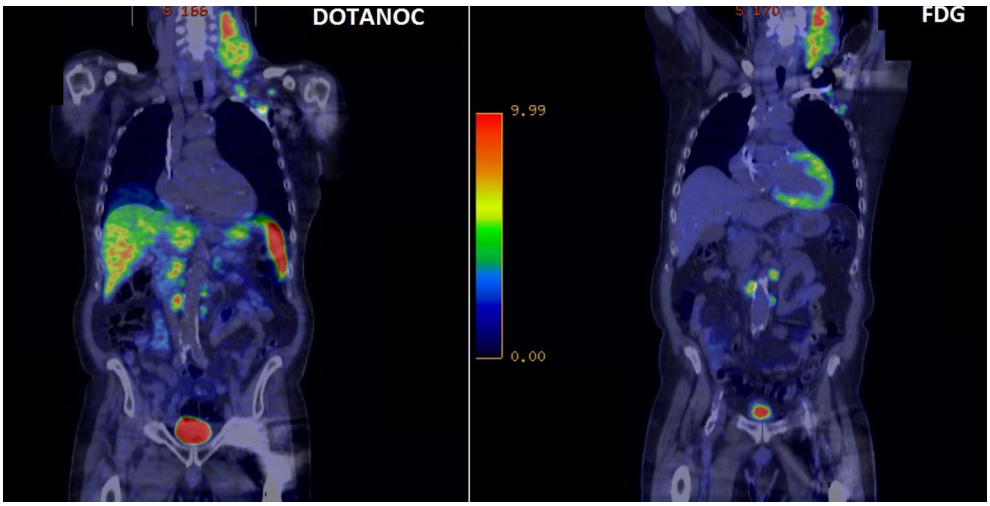

Figure 4. ^{68}Ga-DOTANOC PET/CT and FDG PET/CT of patient No. 19 with nodular sclerosis CHL showing high uptake of ^{68}Ga-DOTANOC at the left cervical, infraclavicular and axillary lymph nodes and additionally at the periaortic lymph nodes.

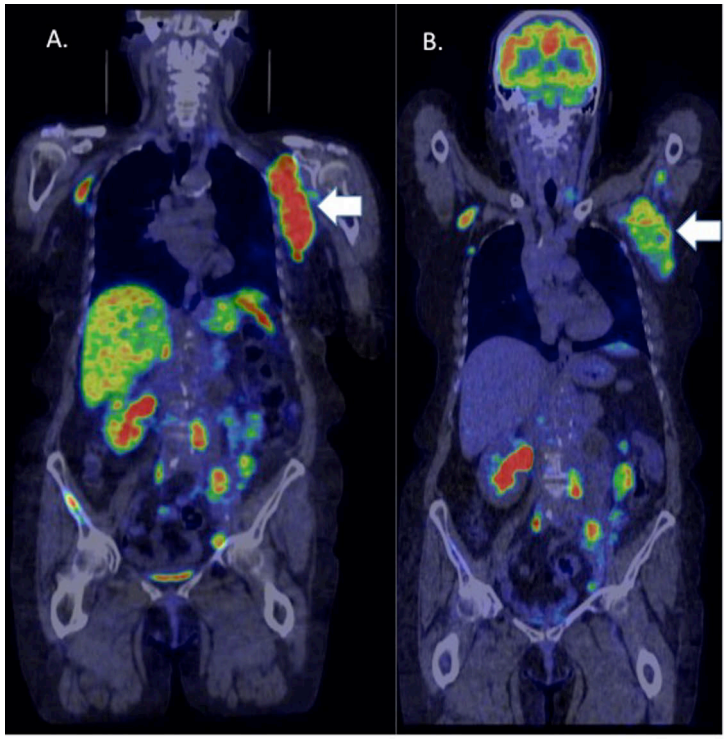

Figure 5. ^{68}Ga-DOTANOC PET/CT (A) of a DLBCL patient (No. 3) with GCB subtype detected lymphomatous lesions with a corresponding pattern than on FDG PET/CT (B). White arrowheads point to a large left axillary nodal lesion with highest SUVmax of 16.5 on ^{68}Ga-DOTANOC PET/CT and 13.4 on FDG PET/CT (modified from Ruuska et al. 2018).

Extranodal lesions were generally ^{68}Ga-DOTANOC-negative, although faint or moderate uptake in bone and bowel lesions was evident in six patients, of whom four had a Krenning score of ≥ 2. Upon visual assessment, two patients (Nos. 4 and 14) presented with uptake of ^{68}Ga-DOTANOC in a non-neoplastic lesion (pelvic abscess and possible pulmonary inflammation). A third patient (No. 18) showed clear uptake in the head of the pancreas, eventually interpreted as a rare cystic form of NET since the corresponding MRI suggested a cystic tumor at the same site. The patient's serum CgA was 2.3nmol/l and a biopsy was not considered, since the patient currently remains symptom-free of a low-grade NET.

5.2.2 Immunohistochemical analysis

5.2.2.1 SSTR2

In SSTR IHC, SSTR2 immunopositivity was demonstrated consistently in macrophages, follicular dendritic cells, and endothelial cells of the veins. All four patients with follicular lymphomas showed SSTR2 immunopositivity in neoplastic follicles (mainly in dendritic cells) (Table 21), but also scattered positivity in the malignant B-cells (Figure 6). Of these patients, two had a positive 68Ga-DOTANOC PET/CT (Table 21, Table 27), which likely was due to tracer uptake in lymphoma related cells and non-neoplastic cells rather than uptake in the malignant B-cells. By contrast, patient No. 3 with DLBCL showed strong SSTR2 immunopositivity in malignant B-cells in agreement with the ^{68}Ga-DOTANOC PET/CT finding (Figure 7). Also, the four other DLBLCs had a positive PET/CT but their SSTR2 immunopositivity was limited to venous endothelial cells, which probably contributed to the positive PET/CT result, since DLBCL has abundant vessel formation associated with neoplastic transformation.

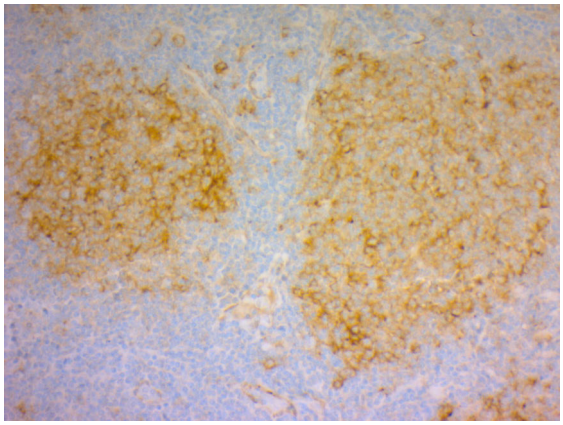

Figure 6. SSTR2 IHC in patient No. 8 with follicular lymphoma showed immunopositivity in the neoplastic follicles and endothelial cells (brown staining).

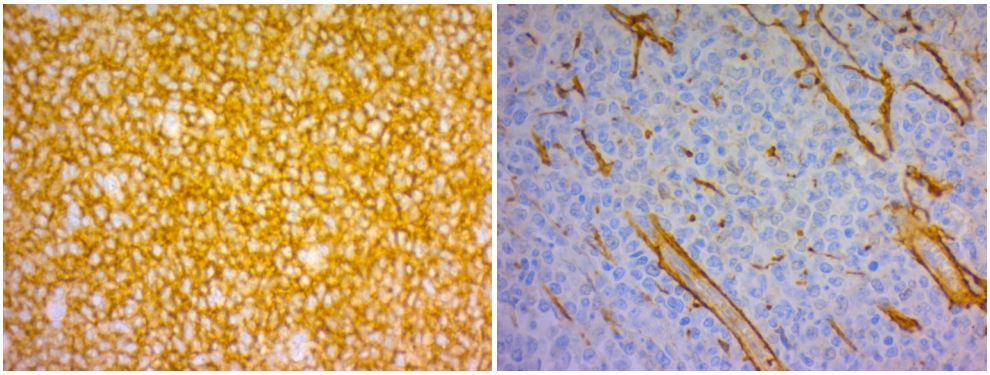

Figure 7. SSTR2 IHC (left) in a DLBCL patient (No. 3) showed immunopositivity in the malignant B-cells (brown staining), whereas SSTR3 IHC remained negative in tumor cells (right). Venous endothelial cells were instead SSTR3 positive (modified from Ruuska et al. 2018).

All four HL patients with successful SSTR2 IHC presented with SSTR2-positive cell membrane of neoplastic Reed-Sternberg (R-S) and Hodgkin cells (Figure 8), although it did not always translate into a positive ^{68}Ga-DOTANOC PET/CT, since only half of these patients had positive findings on SSTR imaging. This is not a surprise, given that R-S cells are scattered and typically few amid a group of lymphocytes and other reactive cells present in lymphomatous tissue. Unfortunately, the fifth case of HL with conspicuous and high uptake of ^{68}Ga-DOTANOC in lymph nodes (No. 19) had unsuccessful SSTR2 IHC (Table 21, Table 27).

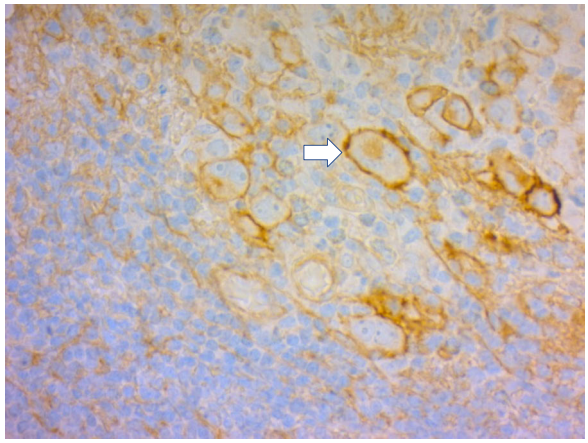

Figure 8. SSTR2 IHC in patient with HL nodular sclerosis (No. 20) showing immunopositivity at the cell membrane of R-S and Hodgkin cells (white arrow).

5.2.2.2 SSTR3

SSTR3 was mainly negative in the malignant cells of all lymphoma subtypes, except for a HL patient (No. 19) who showed SSTR3 immunopositivity in the cytoplasm of R-S cells (Table 21). Some SSTR3 immunopositivity was observed in macrophages, mast cells, and endothelial cells, which could have some impact on uptake of ^{68}Ga-DOTANOC especially in the five DLBCLs where venous endothelial linings stained positive for SSTR3. Another concordant finding was that in the three HLs of the nodular sclerosis subtype, the collagen bands characteristic of this disease showed SSTR3 immunopositivity (Figure 9) possibly contributing to positive ^{68}Ga-DOTANOC PET/CT together with expression of SSTR2 (Table 21, Table 27).

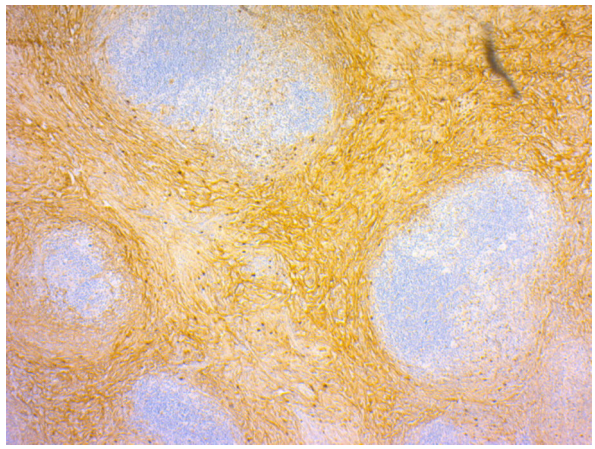

Figure 9. SSTR3 IHC in patient No. 20 with HL nodular sclerosis showing immunopositivity in the collagen bands characteristic of this HL subtype (brown staining).

5.2.2.3 SSTR5

SSTR5 was positive in the malignant cells of a patient with SLL (No. 12) and a patient with HL of the nodular sclerosis subtype (No. 20). SSTR5 was also interpreted as positive in patients Nos. 1 and 19, but their IHC was regarded as unreliable even after repeated analysis. Therefore, their SSTR5 status was left as uncertain. In all other patients, SSTR5 IHC was negative in the malignant cells. (Table 21)

5.2.3 Metabolite analysis

The proportion of unchanged [68Ga]-DOTANOC in venous plasma was almost constant at 15, 45, and 90 min, reflecting good *in vivo* stability of the tracer. One metabolite was detected both in patient and reference samples, which indicates spontaneous degradation of [68Ga]-DOTANOC. The structure of the metabolite was not elucidated.

5.3 SSTR2 and CXCR4 are expressed in DLBCL, FL, and HL (Study II)

5.3.1 DLBCL

Nearly half (46%, n=11) of the DLBCL patients had positive SSTR2 IHC, with strong expression in 73% (n=8) of them (Table 28). SSTR2 expression was located mainly on the cell membrane of the malignant cells (n=10) (Figure 10). SSTR3 and SSTR5 were negative in DLBCL, except for two suspicious cases where SSTR3 was positive in one DLBCL patient (No. 30) who had mild staining in only 5% of the malignant cells, and another patient (No. 40) who had mildly positive SSTR5 IHC, but strong background staining suggested that it might be a false positive.

CXCR4 IHC was positive in 62% of the DLBCL patients, but the staining was mostly mild or moderate. CXCR4 expression was cytoplasmic in all cases and had a specific dot-like pattern in 47% (Figure 10) and a simultaneous expression at the cell membrane in 47% of the cases.

Table 28. SSTR and CXCR4 IHC staining results in DLBCL, FL, and HL in Study II (modified from Juntikka et al. 2021).

Lymphoma	n=	SCORE	SSTR2 n (%)	SSTR3 n (%)	SSTR5 n (%)	CXCR4 n (%)
DLBCL	24	Negative	13 (54%)	23 (96%)	23 (96%)	9 (38%)
		Mild	2 (8%)	1 (4%)		7 (29%)
		Moderate	1 (4%)		1 (4%)	7 (29%)
		Strong	8 (33%)			1 (4%)
FL	22	Negative	10 (45%)			12 (55%)
		Mild	5 (23%)			6 (27%)
		Moderate	2 (9%)			3 (14%)
		Strong	5 (23%)			1 (4%)
HL	18	Negative	8 (44%)	11 (65%)	14 (78%)	4 (23%)
		Mild	3 (17%)	4 (23%)	3 (17%)	6 (35%)
		Moderate	2 (11%)	2 (12%)	1 (5%)	4 (23%)
		Strong	5 (28%)			3 (18%)

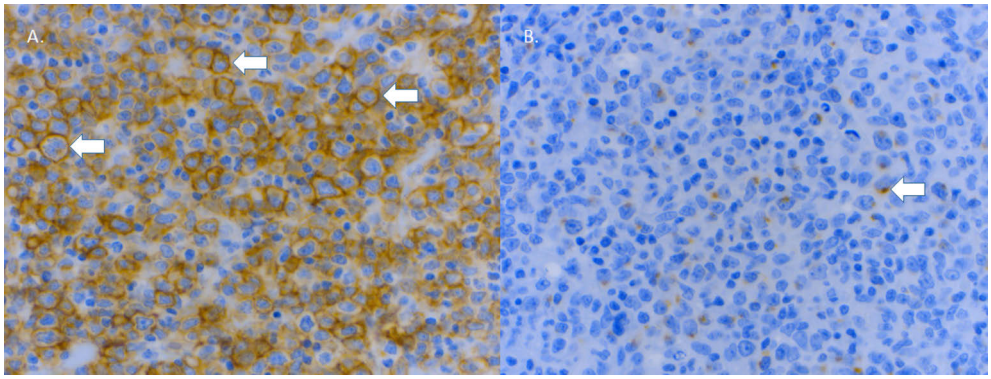

Figure 10. SSTR2 IHC (A) in a patient with DLBCL showing strong immunopositivity at the cell membrane of the malignant cells (arrows), whereas CXCR4 IHC (B) was mildly positive in the cytoplasm of the malignant cells (dot-like staining pattern indicating internalization of the receptor indicated by the arrow).

5.3.2 FL

SSTR2 immunopositivity was observed in 54% (n=12) of the FL patients (Table 28), with the expression located on the cell membrane of the malignant cells in most of the cases (n=7). Three patients had combined membranous and cytoplasmic SSTR2 immunopositivity and two patients had only cytoplasmic, respectively. Forty-five percent (n=10) of the FL patients had positive CXCR4 IHC and, interestingly, here the expression was predominantly membranous (n=8) with few cytoplasmic or combined cases (Figure 11). SSTR3 and SSTR5 stainings were negative in all FL patients. Co-expression of SSTR2 and CXCR4 was present in 41% of the patients (n=9).

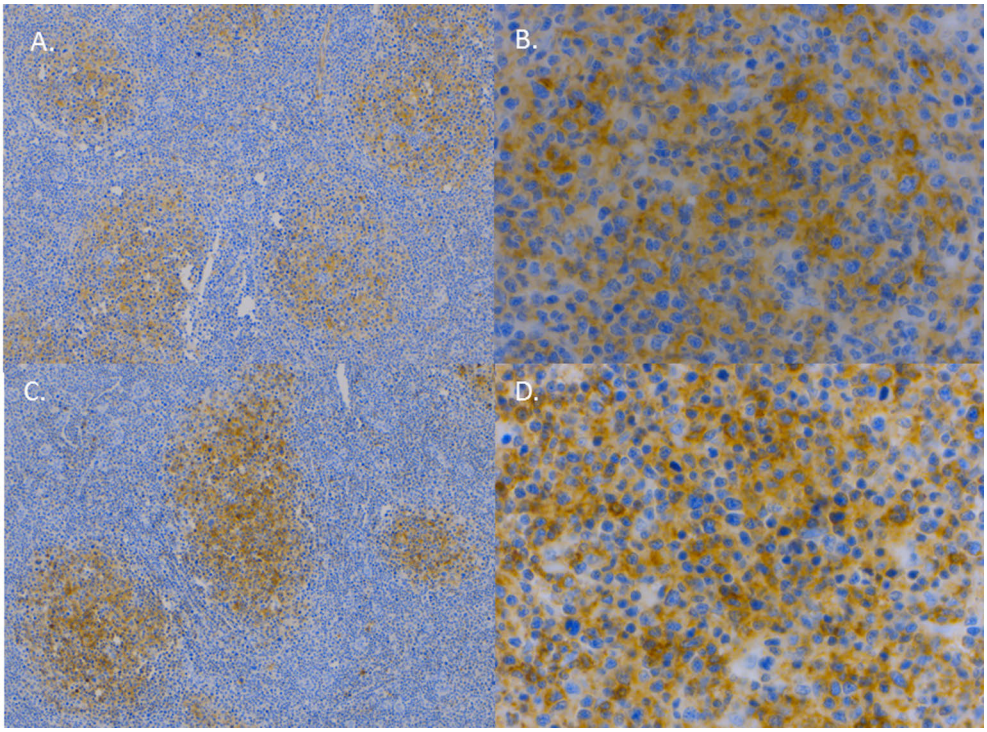

Figure 11. SSTR2 IHC was positive in the cytoplasm and cell membrane of malignant cells in a patient with FL (A, B). SSTR2 immunopositivity was also present in follicular dendritic cells. CXCR4 IHC was positive in the malignant cells, and in follicular non-neoplastic cells (C, D).

5.3.3 HL

A more heterogeneous receptor profile was observed in HL where SSTR2, SSTR3, SSTR5, and CXCR4 IHC were positive in 56%, 35%, 22% and 76% of the cases, respectively (Table 28). The intensity of SSTR2 staining varied, but the majority of the SSTR2 positive patients had immunopositivity at the cell membrane of over 80% of the malignant cells (R-S and Hodgkin cells) (Figure 12). By contrast SSTR3 and SSTR5 expression was located in the cytoplasm. Collagen bands characteristic of HL nodular sclerosis showed SSTR3 immunopositivity in 44% of cases.

CXCR4 staining was often both cytoplasmic and membranous. Homogenous cytoplasmic, homogeneous membranous and dot-like cytoplasmic staining patterns were also observed. Co-expression of SSTR subtypes was evident in a total of three HL cases. Co-expression of SSTR subtypes and CXCR4 was seen in 65% of the HL patients, with SSTR2 being clearly the most common pair. One HL patient (No. 47) had missing SSTR3 and CXCR4 IHC.

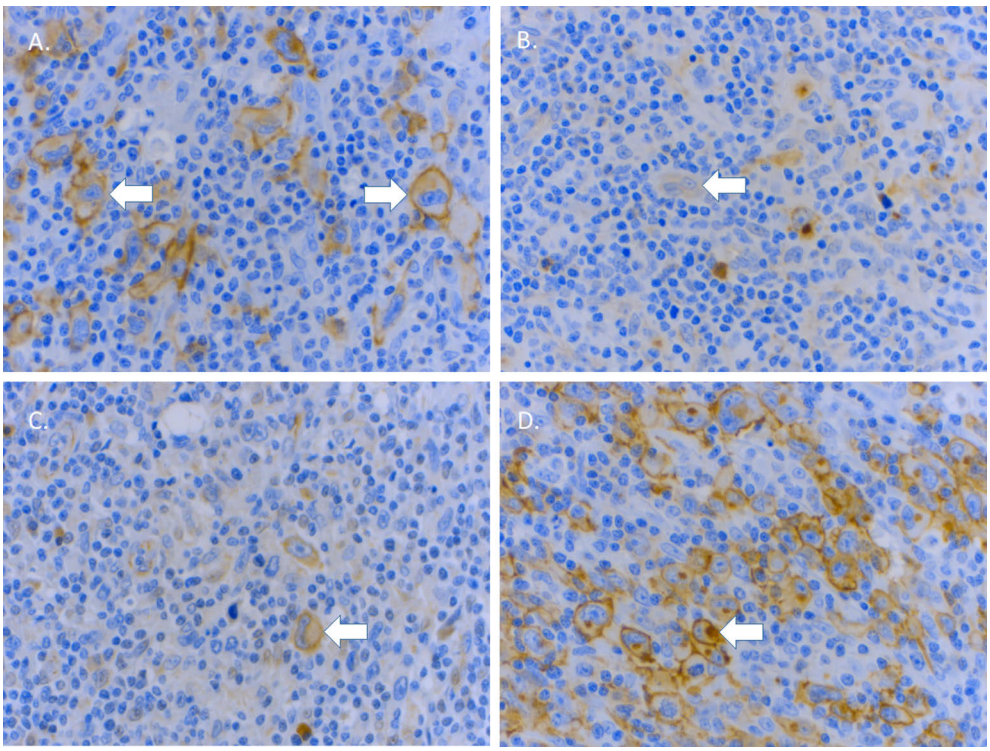

Figure 12. Immunohistochemical stainings of a patient with mixed cellularity HL showed immunopositivity for all receptors. SSTR2 IHC (A) was strongly positive at the cell membrane of R-S and Hodgkin cells (arrows) and also partly in the cytoplasm. SSTR3 IHC (B) and SSTR5 IHC (C) were mildly positive in the cytoplasm. CXCR4 immunopositivity was strong and both membranous and cytoplasmic staining was present (D).

5.3.4 Other lymphomas

A total of five PTCL/ALCL patients had positive findings on IHC stainings. One ALCL patient (ALK-) (No. 93) had positive SSTR2 and SSTR5 IHC and another two had positive CXCR4 IHC (Nos. 92 and 94). One PTCL patient had positive SSTR5 and CXCR4 IHC (No. 90). Interestingly, the only cytotoxic PTCL patient (No. 86) included in the study had strongly positive SSTR5 IHC in 70% of the malignant cells (Figure 13).

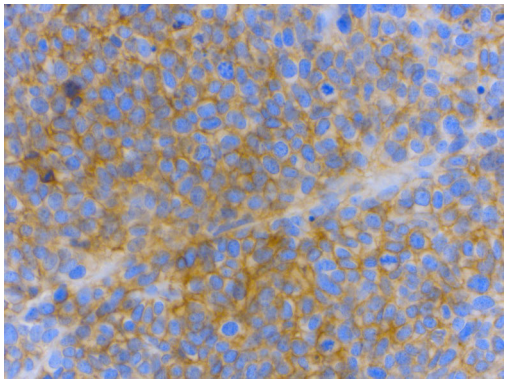

Figure 13. SSTR5 IHC was strongly positive at the cell membrane of malignant cells in a patient with cytotoxic PTCL, while all other receptors remained negative.

Only three MCL patients (15%) had positive IHC results. One patient with a blastoid variant (No. 2) had mild membranous CXCR4 expression. Another patient also with a blastoid variant (No. 6) had mild cytoplasmic dot-like CXCR4 expression accompanied by mild cytoplasmic co-expression of SSTR5. Interestingly, both blastoid variants were found at the nasopharynx, whereas the other two blastoid variants included in this study were nodal diseases and had negative receptor expression. A third patient with a pleomorphic MCL variant (No. 20) had strong CXCR4 expression at the cell membrane of the malignant cells. Unfortunately, the same patient seemed also to have moderate SSTR5 expression, but the result remained inconclusive after repeated analysis. SSTR2 and SSTR3 were negative in all MCL patients.

All MALT lymphomas were negative for all four receptors.

5.4 Epidemiology of CHL and NLPHL in Finland in 1996–2015 (Study III)

5.4.1 Incidence of HL by age, gender, and time trends

In 1996–2015 there were 124 to 182 new HL diagnoses per year (median 139), with a total incidence of 2.54/100 000 person-years (range 2.44–2.65) (Table 29). The incidence of HL was higher in males (2.76/100 000 person-years) than in females (2.34/100 000 person-years) (data not shown). There was a small but statistically significant increase in the incidence of HL during the study period (5-year rate of change 0.3%; 95% CI 0.2 to 0.5). When stratified by gender, the increase in incidence was significant only in males (data not shown).

Table 29. Incidence, mortality, and 5-year estimate of annual percent change in CHL subtypes and NLPHL in Finland in 1996–2015 (modified from Juntikka et al. 2020).

Subtype	Incidence /100 000 (range)	5-year estimate of APC in incidence (95% CI)	Mortality /100 000 (range)	5-year estimate of APC in mortality (95% CI)
Nodular sclerosis	1.57 (1.49–1.65)	0.7 (-0.1–1.4)	0.1 (0.08–0.12)	-1.9 (-5.9–2.3)
Mixed cellularity	0.32 (0.29–0.36)	**-2.2 (-4.0– -0.4)**	0.05 (0.04–0.06)	**2.7 (1.9–3.6)**
NLPHL	0.29 (0.26–0.32)	1.5 (-1.3–4.4)	0.02 (0.01–0.03)	3.3 (-9.9–18.4)
Lymphocyte-rich	0.2 (0.01–0.03)	-0.9 (-5.7–4.3)	0.03 (0.02–0.04)	**-6.4 (-9.8– -2.9)**
Lymphocyte depletion	0.02 (0.12–0.17)	**-6.0 (-10.2– -1.6)**	0.01 (0.01–0.02)	5.4 (-3.1–14.5)
NOS	0.15 (0.12–0.17)	2.0 (-2.9–7.1)	0.07 (0.06–0.09)	**-7.7 (-12.8– -2.3)**
All	2.54 (2.44–2.65)	**0.3 (0.2–0.5)**	0.25 (0.23–0.28)	**-2.8 (-3.8– -1.8)**

Statistical significance is demonstrated as bolded numbers in the estimate of percent annual change (APC) paragraphs with 95% confidence intervals (95%CI).

The age-incidence curve has a bimodal appearance, with the first peak in the young ages and a second one in the elderly (Figure 14). The highest age-specific incidence of HL was observed in the age group of 20–24 years, where the incidence in females and males was 6.2 and 5.4 (per 100 000 person-years), respectively. The second peak in the elderly is wider than the first one and differs between males and females. In males, the second peak is divided into two peaks at the ages of 60–64 and 75–79 years. In females, the second peak is wide and appears in the age group of 70–84 years.

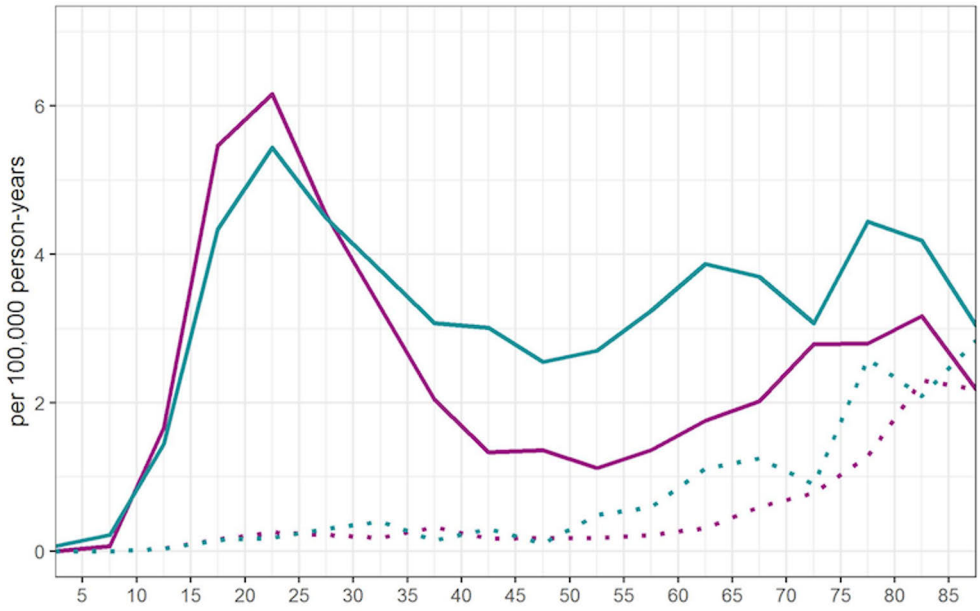

Figure 14. Age-specific incidence (continuous line) and mortality (dotted line) of HL in Finland in males (blue) and females (purple) (modified from Juntikka et al. 2020).

The age-specific incidence of HL did not change significantly over time in 1996–2015 when stratified by age into groups aged 0–14, 15–44 and 45+ years. At the age group of 45+ years, a breakpoint was found (year 2004) after which the 1-year APC was +4.8% (95%CI 2.7 to 7.0) (data not shown).

5.4.2 Incidence by CHL subtypes

5.4.2.1 Nodular sclerosis CHL

The most common CHL subtype was nodular sclerosis (54%), with an incidence rate of 1.57/100 000 person-years (1.40 in males and 1.75 in females, respectively) (Table 29). The incidence of nodular sclerosis CHL remained constant over the study period. Nodular sclerosis CHL was observed mostly in young patients, with only 19% being over 50 years old. The median age of patients was 30 years in males and 27 years in females, and the difference between median ages was statistically significant ($p<0.001$). (Table 26) Interestingly, nodular sclerosis CHL is more common in younger females, but the proportion of males increases at older ages (Figure 15). The age-specific incidence of nodular sclerosis HL increased in the age group of 15–44 years (1-year APC +1.2, 95% CI 0.1 to 2.2) during the study period when stratified by age groups 0–14, 15–44 and 45+ years. In the 45+ age group a

breakpoint was found (year 2004), after which the 1-year APC was +5.9% (95%CI 2.0 to 10.0) (data not shown).

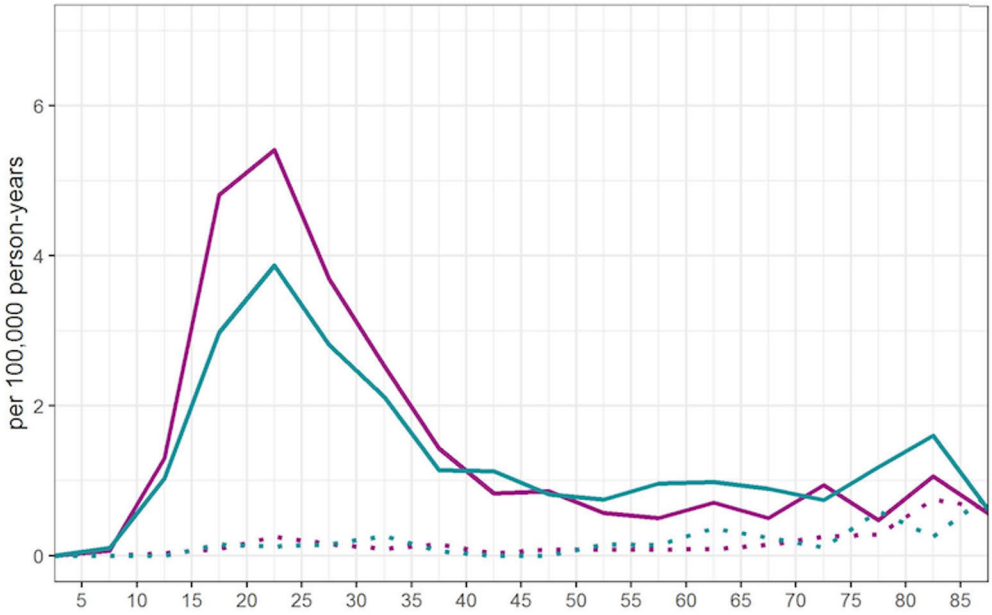

Figure 15. Age-specific incidence (continuous line) and mortality (dotted line) of nodular sclerosis CHL in Finland in males (blue) and females (purple) (modified from Juntikka et al. 2020).

5.4.2.2 Mixed cellularity CHL

The second most common subtype was mixed cellularity CHL, with an incidence of 0.32/100 000 person-years (0.41 in males and 0.24 in females, respectively) (Table 29), and it was more common in males at almost all ages (Figure 16). Mixed cellularity CHL presented mainly in the elderly patients, with 59 % of them being over 50 years of age (Table 26). There was a statistically significant decrease in the incidence of mixed cellularity CHL during the study period (APC -2.1%, 95% CI -3.7 to -0.5). When stratified by gender, the decreasing trend was statistically significant only in females (data not shown).

Age-specific incidence rates showed a decreasing trend in the age group 15–44 years (1-year APC -3.7%, 95% CI -6.8 to -0.6), while there was no significant change in the older population.

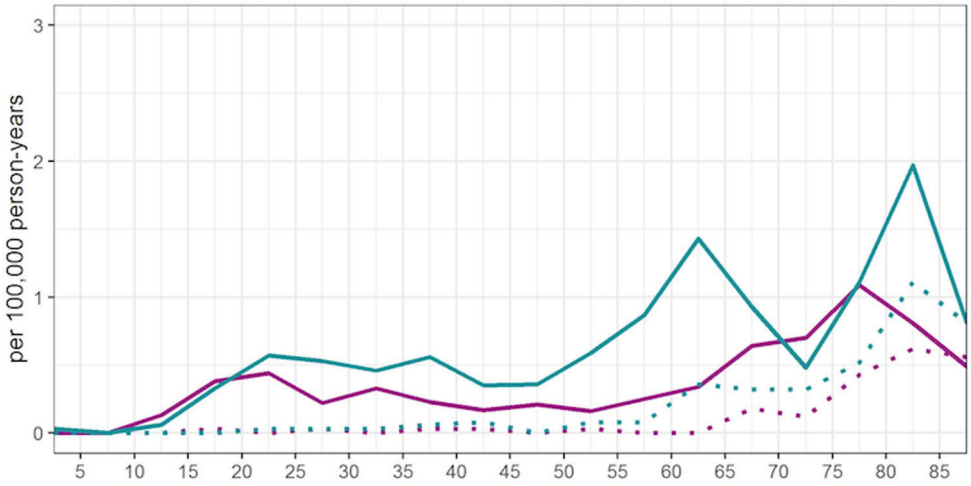

Figure 16. Age-specific incidence (continuous line) and mortality (dotted line) of mixed cellularity CHL in Finland in males (blue) and females (purple) (modified from Juntikka et al. 2020).

5.4.2.3 Lymphocyte-rich CHL

The incidence of lymphocyte-rich subtype was 0.20/100 000 person-years (0.28 in males and 0.11 in females) and it did not change significantly during the study period (Table 29). The median age in males and females was 45 years and 57 years, respectively ($p<0.001$) (Table 26).

5.4.2.4 Lymphocyte-depleted CHL

The lowest number of new cases was observed in lymphocyte-depleted CHL throughout the whole study period, and the incidence was slowly decreasing (5-year rate of change -6.0%, 95% CI -10.2 to -1.6) (Table 29). When stratified by gender this decrease was statistically significant only in males (data not shown). Seventy percent of the patients were over 50 years of age (Table 26), with the highest median age in both males (64 years) and females (66 years) compared to all other subtypes.

5.4.3 Mortality by age, gender, and time trends

HL mortality was 0.25/100 000 person-years during the study period in Finland (0.31 in males and 0.2 in females). There was a statistically significant decrease in mortality both in the 1-year (APC -3.0%, 95% CI -5.0 to -0.9) and 5-year (-2.8%, 95%CI -3.8 to -1.8) rate analysis. (Table 29) The decrease in mortality was statistically significant both in females and in males. Mortality in men was constantly a bit higher throughout the study period and dropped at a slower rate than in women

(data not shown). Age-specific mortality started to increase after the age of 50 in males and after the age of 60 in females (Figure 14).

5.4.4 Mortality by CHL subtypes

Mortality from the nodular sclerosis CHL subtype was 0.1/100 000 person-years, and there was a decreasing trend over the study period albeit not statistically significant (Table 29). When stratified by gender, mortality from nodular sclerosis CHL decreased more rapidly in males, but the decrease remained non-significant (data not shown). The age-specific mortality remained substantially low at all ages in both genders (Figure 15).

Mortality from mixed cellularity CHL was 0.05/100 000 person-years and slowly increased in 1996–2015 (5-year rate of change 2.7%, 95% CI 1.9 to 3.6) (Table 29), but the increase was statistically significant only in males (data not shown). Age-specific mortality started to increase after the age of 55–60 in males and after 60–65 in females, was constantly higher in males, and reached the highest rates in males aged 80–85 (1.11/100 000 person-years) (Figure 16).

In lymphocyte-rich CHL, mortality was 0.03/100 000 and it decreased significantly in both genders over time (5-year rate of change -6.4%, 95% CI -9.8 to -2.9) (Table 29).

The mortality to incidence ratio of lymphocyte-depleted CHL was 0.5 (0.01 versus 0.02 per 100 000 person-years), which indicates that lymphocyte-depleted CHL is an aggressive CHL subtype. There was no change in the mortality trends of lymphocyte-depleted subtype during the study period.

5.4.5 Incidence and mortality of NLPHL

NLPHL accounted for 13% of all HL cases (n=374) in Finland (Table 26). There were no statistically significant changes in the net or gender-specific incidence rates. Age-specific incidence rates showed an increasing trend in the age groups of 15–44 and 45+ years, although the APC remained statistically non-significant. NLPHL was much more common in males than in females (76% males), and males were diagnosed at earlier ages than females with median ages of 45 years and 60 years ($p<0,001$), respectively. Mortality from NLPHL remained stable and substantially low in all age groups and in both genders during the study period. (Figure 17)

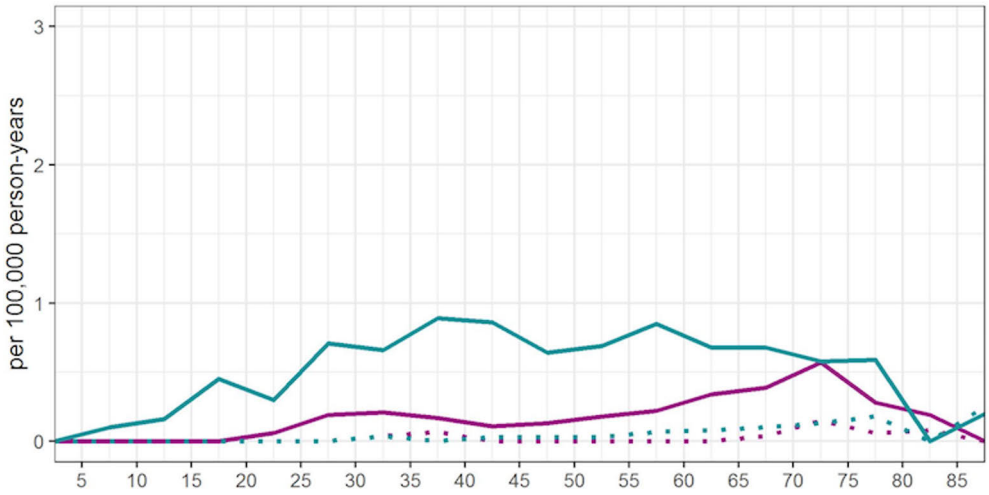

Figure 17. Age-specific incidence (continuous line) and mortality (dotted line) of NLPHL in Finland in males (blue) and females (purple) (modified from Juntikka et al. 2020).

6 Discussion

6.1 SSTRs and CXCR4 in lymphomas (Study I and Study II)

Clinically perhaps the most significant finding of this thesis was that lymphoma should be considered in the differential diagnostics of patients receiving ^{68}Ga-DOTANOC PET/CT for suspicion of a NET. We confirmed in Study I that one patient with a final diagnosis of DLBCL did indeed show strong uptake at ^{68}Ga-DOTANOC PET/CT and her tumor was clearly SSTR2 positive at IHC, supporting the imaging finding. This is consistent with an earlier patient case report where DLBCL mimicked NET at ^{68}Ga-DOTANOC PET/CT (Jain et al. 2014), which prompted us to systematically study SSTR PET/CT imaging in lymphoma. We observed the highest uptake in a patient with nodular sclerosis CHL whose lymphoma showed a median SUVmax of 9.8. As the uptake of DOTA-peptides in NETs is generally much higher, the application of SSTR-based imaging or treatment with PRRT does not seem to be an attractive approach in lymphomas, which was also suggested previously by Dalm et al. 2004. Nevertheless, SSTR-based PRRT could be worth exploring in the palliative treatment of carefully selected cases, considering that lymphomas are generally very radiation-sensitive (Chan et al. 2011), and even lower receptor densities could potentially be sufficient for therapeutic response.

An interesting observation in Study I was that all three nodular sclerosis CHL patients showed detectable uptake in lymphomatous lesions at ^{68}Ga-DOTANOC PET/CT, which is in accordance with earlier studies where high sensitivity in SSTR-based scintigraphy of HLs has been found (Lugtenburg et al. 2001; van den Anker-Lugtenburg et al. 1996). In support of this, IHC of HL in our patients showed SSTR2 immunopositivity at the cell membrane of R-S and Hodgkin cells and SSTR3 immunopositivity at the collagen bands characteristic of the nodular sclerosis CHL subtype. We assume that both SSTR2 and SSTR3 subtypes may contribute to positive ^{68}Ga-DOTANOC PET/CT imaging findings. Positivity in SSTR IHC does not, however, always translate into a positive ^{68}Ga-DOTANOC PET/CT, as was demonstrated in two of our FL and two of our HL patients. In HL, this could be attributed to malignant cells being few, scattered, and surrounded by a large

population of reactive immune cells and stroma. In FL, some malignant B-cells were SSTR2-immunopositive, yet most of the immunopositivity was located in follicles and dendritic cells, as was recently reported also by Tao et. al 2019. In our study, two FL grade 1–2 patients had negative ^{68}Ga-DOTANOC PET/CT and two grade 3A patients had positive scans. We interpreted it to mean that in grade 3A FL patients SSTR2 immunopositivity in lymphomatous cells was the main contributor to scan positivity, but the impact of non-neoplastic cells could not be entirely ruled out. In particular, venous endothelial cell linings were generally SSTR2-positive in our analysis, which could contribute to ^{68}Ga-DOTANOC-positivity in highly vascularized tumors, such as DLBCL.

Our Study I is the first to prospectively evaluate ^{68}Ga-DOTANOC PET/CT imaging in lymphoma and the impact of different SSTR subtypes on tracer uptake. PET/CT has much higher sensitivity compared to scintigraphy used in earlier studies (Ambrosini et al. 2014), and new tracers have emerged, with DOTANOC having a high affinity for SSTR2, 3, and 5 (Virgolini et al. 2010). Earlier studies with SSTR-scintigraphy in lymphomas have reported contradictory results. While some studies reported that SSTR scintigraphy is useful in staging HL (Lugtenburg et al. 2001; van den Anker-Lugtenburg et al. 1996) and extragastric MALT lymphomas (Morgensztern et al. 2004; Raderer et al. 1999; Raderer et al. 2001), others concluded that SSTR scintigraphy does not have a role in diagnosing lymphomas due to low lesion detection rates probably caused by low receptor densities and compromised sensitivity of gamma cameras (Ferone et al. 2005, Ivancevic et al. 1997). Our findings proved that with modern imaging tehniques, lymphomas can be visualized as positive at SSTR-based imaging (^{68}Ga-DOTANOC PET/CT) based on sufficient receptor densities shown by IHC in support of the imaging findings.

We had the impetus to further clarify the expression of SSTRs immunohistochemically in lymphomas in Study II, where we added another interesting target candidate chemokine receptor, CXCR4. Our rationale was to investigate comprehensively the co-expression of SSTR and CXCR4 in multiple lymphoma subtypes, while dual targeting of SSTR/CXCR4 would provide an unforeseen possibility for more efficient radionuclide therapy than targeting each receptor alone. In our analysis, SSTR2 and CXCR4 were expressed in 40–60% of DLBCL and FL patients, SSTR2 abundantly in some cases. In line with our results, SSTR2 expression has recently been shown in 40% of aggressive nasopharyngeal B-NHLs (Chen et al. 2019), and CXCR4 expression in 61% of rituximab-treated DLBCLs (n=56) (Xu et al. 2018), respectively. In a large cohort of 743 *de novo* DLBCLs, 29% were CXCR4 positive (Chen et al. 2015) which is less than in our analysis. Surprisingly, all MALT lymphomas were negative for all studied receptors in our study. In 2016, Stollberg et al. reported that of 55 extranodal MALT-type lymphomas that 92% had positive CXCR4 IHC and 50% had positive SSTR5 IHC.

They used an immunoreactive score described by Remmele and Steigner (1987) for their IHC analysis, which is different from the method used by us in study II, and their antibodies were different from ours as well. We are left to speculate on the differences between their results and ours, but analytical methods seem the most likely cause. Another study showed CXCR4 expression in nodal marginal B-cell lymphomas but not at extranodal lesions such as gastric MALT lymphomas (Deutsch et al. 2013), which is more in line with our results.

In HLs, receptor expression was more heterogeneous, but also here SSTR2 and CXCR4 were the most prominent receptor types, with positive IHC in 56% and 76% of the cases, respectively. SSTR2 was expressed at the cell membrane of R-S and Hodgkin cells as in Study I, whereas in contrast to that study the collagen bands characteristic of HL nodular sclerosis were not consistently SSTR3-immunopositive. SSTR3 immunopositivity was seen in connective tissues in fibroblasts in other lymphomas as well, suggesting that it might not be specific to nodular sclerosis CHL, but further studies are needed in order to determine the role of SSTR3 in nodular sclerosis HL.

Surprisingly, co-expression of SSTR2 and CXCR4 was present in 30–40% of DLBCL, FL, and HL patients, raising questions as to their biological and prognostic role in lymphomas. In NETs and brain gliomas SSTR2 immunopositivity has been associated with better prognosis (Brunner et al. 2017, Kiviniemi et al. 2017). In DLCBL, CXCR4 expression is an adverse prognostic factor and predicts rituximab-resistance, dissemination and disease progression (Laursen et al. 2019, Moreno et al. 2015). Unfortunately, the role of SSTR expression in lymphomas as a prognostic factor is currently unknown, and because of the small number of cases in each lymphoma subtype in Study II, we decided to abstain from survival analysis due to lack of statistical power. More studies of individual subtypes are needed to clarify the biological, clinical and prognostic significance of these receptors and especially SSTR2.

Our studies showed that especially DLBCL, FL, and HL express SSTR2 and/or CXCR4, and the expression was indeed abundant in some cases. These findings mandate further studies focusing on the potential of receptor expression to predict response to SSTR/CXCR4-targeting with PRRT or receptor-mediated drug delivery or therapy resistance. SSTR-based PRRT with ^{177}Lu-DOTATATE has been used successfully in the treatment of metastatic midgut NETs and is now clinical practice while it confers a significant PFS advantage over injected somatostatin analogues used alone (Strosberg et al. 2017). Furthermore, PRRT is considered as a safe treatment method with few adverse effects (Ivanidze et al. 2019), making it patient-friendly while maintaining a high health-related quality of life. As of now, one nonradioactive CXCR4 antagonist, Plerixafor, has been approved for clinical use for stem cell apheresis in lymphoma, and the first PRRT-based CXCR4-targeted

radiolabeled agents, such as ^{177}Lu-pentixather, are undergoing clinical evaluation. CXCR4 antagonists could be promising for treating CXCR4-expressing lymphomas failing on rituximab, while CXCR4 antagonists might circumvent resistance to rituximab (Laursen et al. 2019, Reinholdt et al. 2016).

6.2 Incidence and mortality of CHL subtypes and NLPHL in Finland in 1995–2015 (Study III)

The epidemiology of HL subtypes has not previously been studied in Finland, since current cancer coding guidelines did not recognize HL subtypes until 2007 when the ICD-O-3 was introduced at the FCR. The five different HL subtypes have distinct clinical, histological and prognostic characteristics and are classified as separate disease entities in the WHO classification (Swerdlow et al. 2017). Hence, it was important to update HL NOS codes to match the current classification criteria, which enabled longer-term epidemiological statistics from five different HL subtypes.

In Finland, in 1995–2015 the total incidence of HL increased slightly while the mortality was dropping. Earlier studies have reported decreased mortality in HL as well, which probably reflects improved diagnostics and treatment options. By contrast, the incidence of HL has been either declining or stable in other Western countries (Hjalgrim et al. 2001, Morton et al. 2006, Sjöberg et al. 2012). Nodular sclerosis CHL was the most common subtype and was mainly seen in young adults, as was reported in earlier studies (Glaser et al. 2015; Shanbhag & Ambinder 2018). The overall incidence of nodular sclerosis CHL remained constant during the study period in Finland, yet the age-specific incidence rates increased in the age group of 15–44 years, and after year 2004 also in the age group of 45+ years. This observation is clearly in contrast to an earlier report from the Nordic countries covering the period 1987–1997 (Hjalgrim et al. 2001), where the incidence of nodular sclerosis CHL increased significantly in younger population. Also a more recent study from the United States reported that the overall incidence of nodular sclerosis CHL was dropping throughout 2007–2011 (Glaser et al. 2015). For some reason, the incidence of HL has been higher in Finland than in the other Nordic countries (Storm et al. 2010). It is possible that also differences in study timelines, study populations (i.e., divergent ethnicity and exposure to HL risk factors), or cancer registries could in part contribute to the differing results between epidemiological studies.

Mixed cellularity CHL was the second most common subtype in Finland, and the incidence was decreasing but mortality was increasing, which could be attributed to elderly males having the highest age-specific incidence rates and 59% of patients being over 50 years of age. It our study, NLPHL was the third most common HL subtype and accounted for 13% of all HLs, which is clearly higher compared to earlier reports from Western countries (Glaser et al. 2015; Morton et al. 2006;

Nogova et al. 2008) but in good coherence with another Finnish study where the incidence of NLPHL was 16.6 % (Saarinen et al. 2013). The reason for the higher incidence of NLPHL in Finland remains unclear to us and requires further study to obtain clarification.

Although HL is known to be common in young adults, our study showed that 36% of the patients were over 50 years old. Elderly patients are known to a poorer prognosis and more limited treatment options, which makes the treatment more challenging. Elderly HL patients should therefore be acknowledged in future studies as a patient group needing new, more tolerable treatment methods (Sjöberg et al. 2012).

According to our analysis, HL subtypes have distinct epidemiological patterns which could reflect their biological heterogeneity. At its best, epidemiological information could help in finding etiological factors contributing to lymphoma development. (Morton et al. 2006) Further studies are warranted the search for underlying etiological factors that could explain the heterogeneity of HL.

6.3 Study limitations

The major limitation of Study I was the lack of histological confirmation of all ^{68}Ga-DOTANOC positive lesions. Due to presence of multiple lesions, biopsy of all these would have been both impractical and unethical. We therefore used FDG PET/CT as the gold standard, where increased tracer uptake coupled with a suitable anatomic location and morphologically suspicious mass or lesion was regarded as a tumor. Faint or moderate uptake was seen in six patients in extranodal bone or bowel lesions. Also, one patient had a lesion deemed as inflammatory in the lung and another patient had a pelvic abscess which disappeared with antimicrobial treatment. Still, it is possible that some false FDG-positive lesions and/or lesions misinterpreted as non-neoplastic were included in our evaluation, where interpretation of the uptake of ^{68}Ga-DOTANOC was performed by recognizing the known pitfalls such as focal physiological uptake in the pancreas, accessory spleen, osteoblastic activity, inflammation, or infection (Hofman et al. 2015; Virgolini et al. 2010). The second limitation was failure of SSTR5 IHC in two patients and of SSTR2 in one, respectively, which leaves some uncertainty as to the possible impact of these failures on imaging results. Finally, we included all lymphoma subtypes in this pilot study, which prevented us from any statistical analysis in each histological subtype because of small subgroup size.

The are some limitations to Study II. First, the SSTR5 antibody did not work reliably even after trying multiple dilutions. Although a new batch was later received we did not stain all the samples again, but only those for which the first antibody had not given a conclusive result. There is always some uncertainty present when

performing IHC stainings, as the staining is affected by i.e., with the quality of the tissue sample and antibodies used, which should be noted when analyzing the results of similar studies. Second, as a standardized evaluation system for analyzing SSTR and CXCR4 expression in lymphomas is lacking, we developed our own score for evaluating receptor expression in IHC stainings. Third, our patient material was overall fairly heterogeneous due to small subsets of patients in each selected lymphoma subtype, and additionally also relapsed and transformed diseases were included. Statistical analysis of receptor expression and prognosis in the whole study population as a one group was not pursued, since all selected lymphoma subtypes represent separate disease entities.

The limitations of Study III include the use of registry data, which is known to have some disadvantages (Pukkala et al. 2018). Histological re-analysis of tissue samples was not performed, as we relied on the information in pathology and clinical reports when re-coding HL NOS morphology codes into specific HL subtypes. Also, the pathologists who had analyzed the tissue samples over the years were not all specialists in hematopathology, which is known to affect diagnostic accuracy (Proctor et al. 2011; Stevens et al. 2012). The small number of patients in the HL subtype groups renders statistical analysis prone to errors especially when stratified further by age, gender, and time, and caution should be used when interpreting such results. Finally, we were able to recode only 35 Hodgkin NOS morphology codes out of 151 from years 2007–2015 (when the ICD-O-3 was used at the FCR). The original pathology report often stated that that the biopsy material was insufficient, or it included two classification choices. Single coding errors were also noticed. These are in line with a similar report from the U.S. (Glaser et al. 2015).

6.4 Future prospects

Knowledge on the heterogeneity of lymphomas, even within a well-characterized histologic subtype, continues to grow. New molecular research and the expansion of existing knowledge is creating a need to develop lymphoma classification alongside new diagnostic and treatment methods. Personalized medicine approaches targeting specific molecules are gradually becoming the new standard complementing the basic chemotherapy regimens which remain the cornerstone of treatment. It would be of significant interest to consistently determine the expression of two peptide receptors, SSTR2 and CXCR4, in a large population. This thesis indicates that at least in DLBLC, FL and HL their expression is common and may modify the response to a variety of lymphoma treatments. As both SSTR2 and CXCR4 fit perfectly within the theranostic paradigm, it is foreseen that targeting of these receptors will be an arena of intensive research in the future.

7 Conclusions

Study I: Some malignant lymphomas are positive in ^{68}Ga-DOTANOC PET/CT imaging and should hence be recognized in the differential diagnosis of NETs as a potential source of false diagnosis. Positivity at ^{68}Ga-DOTANOC PET/CT is likely due to SSTR expression in malignant cells, notably in DLBCL and HL, or in adjacent cells contributing to lymphoma development (i.e., venous endothelial cells and collagen bands). As lymphomas are highly sensitive to radiation, this occasionally abundant SSTR expression in DLBCL and HL may even pave the way for developing SSTR-based treatments in the future.

Study II: Approximately half of all DLBCL, FL and HL patients express SSTR2, which is often co-expressed with CXCR4. SSTR2 expression was strong in 73% of the SSTR2-positive patients in DLBCL, showing that also abundant expression exists. In DLBCL and FL, SSTR3 and SSTR5 IHC were negative, while in HL the receptor expression was more heterogenous. Fifteen percent of the MCL patients had positive CXCR4 IHC, which was sometimes accompanied by SSTR5 expression. PTCLs expressed SSTR2, SSTR5, and CXCR4 randomly, but an observation of note is that the only cytotoxic PTCL variant had the only strong SSTR5 IHC. MALT lymphomas were negative for all receptors. Lymphomas with abundant SSTR2/CXCR4 expression could be candidates for trials studying SSTR2 and/or CXCR4 based treatments in the future.

Study III: HL incidence slowly increased while the mortality decreased in Finland in 1996–2015. Nodular sclerosis CHL was the most common subtype, followed by mixed cellularity CHL and NLPHL, with the latter representing 13% of all HLs diagnosed in Finland. Over one third of HL patients were over 50 years of age representing a patient population in need of new and better-tolerated treatment options.

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