Mechanisms of Disease 2

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Preface

Throughout history, concepts of the causes of disease have gone hand in hand with contemporary knowledge. Around 2500 B.C. a disease was considered to be a patient’s own fault, or the result of an intervention by gods, demons or spirits. From 300 B.C. until about 1500 A.D., clinical observations and autopsies (gross, morbid or macroscopic anatomy) led to new concepts about the origin of disease. In this period, the cause of a disease was attributed to an imbalance in the bodily fluids (humors). From 1500 until about 1800, diseases were often believed to be a consequence of spontaneous generation of pathogens from dead material (abiogenesis). It was not until the nineteenth century that Rudolf Virchow put forth the idea that disease was caused by alterations in cells. Nowadays, the concept of disease can be summarized as follows: molecular changes lead to cellular changes that result in tissue (organ) changes and subsequently cause clinical signs and symptoms.

To improve our understanding of clinical diseases knowledge about the cause (etiology), the underlying mechanism (pathogenesis) by which the disease develops, and the ultimate structural and functional changes of cells, tissue and affected organs is essential. In the first 12 weeks of the second year of this new curriculum the major mechanisms of disease are discussed (fig.1). In the first six week (G2MD1), the focus was mainly on inflammation, cell and tissue injury and repair and disordered immunity. In this module (G2MD2) the mechanisms of neoplastic growth disorders and hemodynamic disorders (hemostasis, bleeding and thrombosis) will be the focus in relation to the clinical presentation of the disease, diagnostic procedures and treatment modalities.

The multidisciplinary approach in this module is illustrated by the number of participating departments such as Human Genetics, Clinical Genetics, Pathology, Clinical Oncology, Hematology, Gynecology, Pulmonology, Surgical Oncology and Pharmacology.

Neoplasia literally means ‘new growth’. A new growth is called a neoplasm or tumor. The term tumor was originally applied to a swelling caused by inflammation, but is now often used to refer to neoplasms. Oncology (Greek oncos means tumor) is the study of neoplasms. An accurate definition of the term ‘neoplasm’ is: ‘A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after cessation of the stimuli which evoked the change.’ The abnormal mass is purposeless, preys on the host, and is virtually autonomous. Tumors are either benign or malignant, and cancer is the common term for all malignant tumors.

During this part of the course the student gains insight into the relation between genetic alterations in cells and morphologic changes in the affected cells and tissues. Students will learn how genetic changes lead to tumor development including the hereditary basis of certain types of cancer. Furthermore, the classification of tumors (tumor types), the tumor cell characteristics that lead to metastasis, and tumor diagnosis will be discussed. Attention will be paid to grading and staging systems. Based upon these findings the multidisciplinary approach of many aspects of curative and palliative treatment options in a variety of malignancies (e.g. breast, colorectal, non-small cell lung (NSCL), prostate, melanoma, cervical, endometrial and hematological cancers) will be discussed.

The mechanism of disease “Hemodynamic disorders” (fig.1) will introduce you to the major clinical symptoms in the disturbance of the maintenance of blood flow and to their underlying mechanisms. Primary and secondary hemostasis, thrombosis and atherosclerosis are discussed as main mechanisms of this disorder. Finally, thrombosis as paraneoplastic phenomenon in relation to cancer will be discussed.
The course-committee who has developed this module Mechanisms of Disease 2 wishes you an enjoyable learning experience.

Figure 1

NOTE
This module book contains a number of color images but it was not possible to print in color. To view the color images please use the PDF of the module book which is available on Blackboard.
0. Introduction and general information

0.1 Introduction to the module Mechanisms of Disease 2

This course elaborates on the first year modules of Medicine in which the normal anatomy, physiology and homeostasis were taught. Disease is the result from a disturbance in the structural integrity and/or normal function of (part of) the body and/or the response to this disturbance. In this module (Mechanisms of Disease 2, G2MD2) the focus is mainly on the mechanisms of neoplastic growth disorders (development of cancer) and hemodynamic disorders (thrombosis, atherosclerosis and bleeding disorders). Some overlap with other mechanisms of disease may occur.

0.2 Themes and subthemes

The module is organized in 6 main themes which together cover the subjects for study in coherent components and determine the structure and contents of the module.

Mechanism of disease: Growth disorders
1 The etiology of malignancies
   a Genetics and epigenetics
   b Cancer biology
   c Hereditary cancers
   d Environmental factors
2 Nomenclature, staging principles and basics in treatment modalities and decisions of malignancies
   a Nomenclature
   b Diagnostic procedures and staging principles
   c Basic treatment modalities and decisions
   d Heterogeneity in cancer behavior
   e Palliative treatment
3 Clinical and pathological aspects of the most frequent types of malignancies (70-80%); breast cancer, colorectal cancer, non-small cell lung cancer (NSCLC) and prostatic cancer
   a Breast cancer
   b Colorectal cancer
   c Non-small cell lung cancer
   d Prostatic cancer
4 Clinical and pathological aspects of hematological malignancies
   a Hematopoiesis
   b Leukemia
   c Lymphoma
5 Psychosocial aspects of cancer, palliative and supportive care, organization of cancer healthcare and alternative medicine (quackery)
   a Complementary medicine
   b Cancer health care
   c Psychosocial aspects
   d Screening, counseling and follow-up
   e Palliative care
Mechanism of disease: Hemodynamic disorders
6 Thrombosis and Atherosclerosis
   a Hemostasis
   b Thrombosis
   c Atherosclerosis

0.3 Learning objectives

Main learning objectives

The student:
- understands the major aspects of the etiology, pathogenesis and pathophysiology of neoplasia
development and progression at the molecular, cellular, tissue, organ and patient level.
- identifies the basic mechanisms of disease in the development of malignancies and hematological
disorders including hemodynamic disorders (e.g. thrombosis).
- describes the differences between benign and malignant tumors.
- understands the principles of tissue invasion and lymphogenic and hematogenic metastasis.
- knows how to diagnose, stage and treat patients with malignancies.
- relates the choice of treatment to the patients physical condition, mental status and social
circumstances.
- describes the short and long term effects of cancer diagnosis and treatment.
- knows how cancer care in the Netherlands has been organized, including terminal and palliative care.

Learning objectives per theme

Theme 1: The etiology of malignancies
The student:

a specifies the role of mutations, epigenetic changes, viruses and environmental factors in the
development of malignancies (tumorsuppressorgen (TSG), oncogenes, types of mutations, familial
cancers (Knudson), Human Papilloma Virus (HPV), epigenetics, genomic instability).
b describes the mechanism of differentiation of stem cells to end-stage highly differentiated cells and
the regulation of this process by cytokines/growth factors and their receptors and the physiological
response to endo- and exogenous factors such as stress responses and infection, respectively.
c explains the differences between normal and abnormal growth and regulation and dysregulation of
the hematopoietic cell system.
d provides an overview of the cellular defense mechanisms against cancer (DNA damage, DNA repair,
cell cycle checkpoints, apoptosis, immune system).
e denominates the processes that initiate and influence tumor growth and relates these to the
morphological changes in a tumor cell.
f can explain the impact on patient care and the ethical consequences of genomic analysis of tumors
and genetic screening of patients (whole genome sequencing, gene expression analysis, exome
sequencing, germ line mutations, variants of uncertain significance).
g can distinguish (pathologically and clinically) between benign and malignant tumors, and name the
differences.
h can specify the properties of tumors that can serve as guidance for therapeutic purposes (rate of cell
proliferation, highly specific mutations, gene expression profiles, protein expression and production).
Theme 2: Nomenclature, staging principles and basics in treatment modalities and decisions of malignancies

The student:

a. is able to use appropriately the oncologic vocabulary regarding benign and malignant tumors and their pre-malignant stages.
b. describes the difference between grade and stage of malignancies.
c. understands the mechanisms by which malignant tumors can metastasize and knows the differences between metastatic spread via lymph nodes, blood vessels or per continuitatem.
d. describes and applies in given cases the principles of staging of cancer and knows the differences between different staging classifications (TNM, FIGO, Ann Arbor, Breslow, WHO 2008, Rai/Binet).
e. understands the principles and differences between the different diagnostic modalities: cytology/histology, immunophenotyping (FACS-analysis), cytogentetics, FISH, and gene-expression profiles and how to apply these tests in clinical cases.
f. describes the principles and methods used for appropriate staging of patients with malignancies (CT/MRI/ECHO/PET-CT).
g. describes the different aspects and intentions of anti-cancer treatment modalities (curative vs palliative, local control vs systemic control, adjuvant vs neoadjuvant, combination of modalities)
   • surgery (R0/1/2, organ saving procedures, palliative surgery),
   • medical oncology (including targeted therapies, mechanism of action of chemotherapy, iv vs orally administered, hormonal treatment, concept of micrometastatic disease)
   • radiation oncology (primary treatment, elective treatment, chemoradiation, therapeutic window, local treatment, technical issues)
h. incorporates the clinical condition of a patient in the therapeutic decisions and knows how to assess this condition (age, co-morbidity, previous operations, social network, WHO-stage, Karnofsky-score).
i. understands the impact of morbidity, complications and possible mortality of anti-cancer treatment and the trade-off between these and the treatment intention (cure, palliation, prolongation of life)
j. can apply the additive value of genetic and epigenetic alterations to improve risk assessment in the individual patient.

Theme 3: Clinical and pathological aspects of the most frequent types of malignancies (70-80%); breast cancer, colorectal cancer, non-small cell lung cancer (NSCLC) and prostatic cancer

The student:

a. describes the genetic and epigenetic abnormalities in these four cancer types and understand those alterations in relation to morphological tissue changes leading to cancer.
b. knows the hereditary aspects of cancer especially in colon cancer and breast cancer and which genes are involved and applies this knowledge into clinical practice (genetic counseling, screening high risk groups, subtotal colectomy, preventive surgery).
c. recognizes the common clinical presentations of these four cancer types and describes the main treatment options of these four tumor types.
d. understands the relevance of the differences in clinical behavior of those malignancies and applies this knowledge in the workup treatment and follow-up (prostatic vs lung cancer, metastatic breast cancer vs metastatic colorectal cancer, selective use of tumor marker analysis etc).
e. describes several aspects of the impact of a hereditary tumor on the social and psychological condition of a patient and his family.
f. has knowledge of the principles, benefits and drawbacks of population cancer screening and can use the arguments in a discussion.
has knowledge of different palliative interventions (e.g. supportive care, pharmacological and non pharmacological, including analgetics and anti-emetics).

can integrate the knowledge regarding the etiology of cancer, insight in the heterogeneity of the disease, accompanying symptoms, impact of the diagnosis on clinical well-being and treatment modalities into an understanding of a clinical case and a proposal for individualized treatment and counseling.

**Theme 4: Clinical and pathological aspects of hematological malignancies**

The student:

a. understands the regulation of the normal growth pattern of the hematopoietic system and the physiological responses to endogenous and exogenous stimuli.

b. can describe the main differences in clinical presentation, physical examination, laboratory findings and imaging modalities in the most important hematological malignancies (e.g. acute and chronic leukemia and lymphomas).

c. knows the approach to analyze clinical presentations such as anemia, leukemia, based upon the knowledge described above.

d. knows the basic treatment modalities in hematological malignancies (stem cell transplantation, targeted therapy, chemotherapy and radiotherapy).

**Theme 5: Psychosocial aspects of cancer, palliative and supportive care, organization of cancer healthcare and alternative medicine (quackery)**

The student:

a. will learn the importance of communication and working together in a multidisciplinary cancer treatment team.

b. will learn how the Dutch healthcare system works for cancer patients and will hear the pros and cons of centralization of cancer care.

c. will explore the existence of alternative treatment modalities in cancer patients and the pros and cons of those in cancer treatment.

d. will learn about the definitions of palliative and supportive care, about palliative treatment options, quality of life issues such as care for remaining life, the dying phase, the use of medication for pain and other symptoms, palliative sedation and euthanasia.

**Theme 6: Thrombosis and atherosclerosis**

The student:

a. understands the role of the vessel wall, endothelium, thrombocytes and plasma factors in hemostasis and the role of pro- and anticoagulant factors.

b. understands the principles and mechanism of balance between thrombosis and hemorrhage.

c. is able to explain in clinical cases which component of hemostasis is disturbed and knows which clinical tests can be used to identify this.

d. can describe the differences between congenital and acquired diseases of thrombotic disorders.

e. can explain the principles of pharmacological interventions targeting coagulation.

f. relates clinical aspects and epidemiology of thrombosis to cancer and the mechanisms playing a role in thrombosis as a paraneoplastic phenomenon.

g. can describe the mechanism by which atherosclerosis develops in vessels and which factors are involved in and predispose for this condition (e.g. radiotherapy and chemotherapy).
0.4 Competences

From the CanMeds roles framework four competences are explicitly addressed in the module G2MD2, which will be further elaborated on in the line courses:

**Medical Expert**

The student will learn to identify the mechanisms in the development of malignancies and hemostatic disorders and to choose appropriate diagnostic tests, explain the pathogenesis and apply the basic concepts of treatment of malignant and hemostatic diseases.

**Health Advocate**

Physicians should be able to respond to individual patient health needs and issues as part of patient care. Moreover, they should be able to respond to the health needs of the community that they serve. Finally, the role of environmental factors (determinants of health), such as smoking, diet, sexual behavior, and hormonal factors that may contribute to the development or prevention of several types of cancers and hemodynamic disorders will be discussed. This will help the student to become a true health advocate.

**Scholar**

The correct interpretation of (clinical) scientific publications is an important component of the life-long medical learning process. In the treatment of cancer and thrombosis evidence-based medicine does play a crucial role. This competence will be trained in several work groups and the debates organized during this course. Finally, important and interesting historical developments in the field of cancer and hematological diseases are presented.

**Collaborator**

The multidisciplinary approach in cancer treatment requires an interprofessional health team. You should be able to work effectively and appropriately with other health professionals to prevent, negotiate and resolve interprofessional disputes/conflict.
0.5 Prerequisites

- Knowledge of the structure of the normal human cell and the most important physiological and biochemical processes of the cell
- Knowledge of the normal histology of tissues and organs
- Knowledge of the concepts molecular recognition, receptor-specificity, receptor-ligand interaction
- Understanding normal regulation of blood pressure and temperature
- Insight into causes and mechanisms of pain sensation
- Knowledge of epidemiological terminology
- Usage of English at level B2 (Common European Framework of Reference for Languages)

0.6 Place of Module Mechanisms of Disease 2 in the Curriculum Bachelor of Medicine

The concepts learned in module G2MD2 will be used in all subsequent modules that address clinical problems (vraagstukken). In subsequent modules additional specific diseases will be addressed, expanding the differential diagnostic potential of the student for which a basis was laid in module G2MD2.
### 0.7 Exam(s): material and matrix

The content of all lectures (LT/RL), self-study assignments (SSA and COO), work groups (WG), interactive sessions (IS), case discussions and the pages of the study books as indicated in the individual reading lists are all part of the exam material. The information labeled “additional” in the reading lists can be used to prepare the SSA, COO, WG and IS but is NOT part of the exam material.

This exam matrix gives you a rough indication of the proposed distribution of exam questions (minor deviation is possible).

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<td>a. Genetics and epigenetics</td>
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<tr>
<td>b. Cancerbiology</td>
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<td>5</td>
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<td>c. Hereditary cancers</td>
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<td>6</td>
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<tr>
<td>d. Environmental factors</td>
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<td><strong>2. Nomenclature, staging principles and basics in treatment modalities and decisions of malignancies and metastases</strong></td>
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<td>a. Nomenclature</td>
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<td>b. Diagnostic procedures and staging principles</td>
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<td>d. Heterogeneity in cancer behavior</td>
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<td>e. Palliative treatment</td>
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<td><strong>3. Clinical and pathological aspects of the most frequent types of malignancies</strong></td>
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<tr>
<td>a. Breastcancer</td>
<td>2</td>
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<td>b. Colorectal cancer</td>
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<tr>
<td>c. Lung cancer</td>
<td>1</td>
<td>4</td>
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<td>d. Prostatic cancer</td>
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<td><strong>4. Clinical and pathological aspects of hematological malignancies</strong></td>
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<td>a. Hematopoiesis</td>
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<td>3</td>
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<tr>
<td>b. Leukemia</td>
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<td>4</td>
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<tr>
<td>c. Lymphoma</td>
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<td><strong>5. Psychosocial aspects of cancer, palliative and supportive care, organization of cancer healthcare and alternative medicine (quackery)</strong></td>
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<td>a. Complementary medicine</td>
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<td>b. Cancer health care</td>
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<td>c. Psychosocial aspects</td>
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<td>d. Screening and follow-up</td>
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<td>e. Palliative care</td>
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<td><strong>6. Thrombosis and atherosclerosis</strong></td>
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<tr>
<td>a. Hemostasis</td>
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<tr>
<td>b. Thrombosis</td>
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<td>3</td>
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<td><strong>Total points</strong></td>
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<td><strong>100</strong></td>
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0.8 Assessment

In this module, assessment consists of two summative tests: one mid-point exam (20 points) and a large final exam (100 points), each of which contributes to the grade.

Mid-point exam (max. 20 points)

There will be a mid-point exam half way the course.
- Date: Monday November 4th, 09.00-10.00 (week 4), different versions
- Duration: 60 minutes
- Subjects: all lectures, COO, self-study assignments, work groups and interactive sessions contents, plus indicated pages from the study books of the first 3 weeks.
- Competences: Medical expert (80%), Health advocate (10%), Scholar (10%)
- Type: This mid-point exam will consist of 20 multiple choice questions

NOTE. Participation in this mid-point exam is voluntary, thus NOT a prerequisite for release of the final grade. If this mid-point exam is missed this implicates 0 points for this component, there is no opportunity for a re-exam of this mid-point exam during this module.

Final exam (max. 100 points)

- Date: Friday November 22nd, 09.00-12.00 (week 6), different versions
- Duration: 180 minutes
- Subjects: all lectures, COO, self-study assignments, work groups and interactive sessions contents, plus indicated pages from the study books
- Competences: Medical expert (80%), Health advocate (10%), Scholar (10%)
- Type: The final exam will consist of multiple choice questions, extended matching questions and open questions

For distribution of questions per theme see page 15 Exam matrix.

The total number of points for the mid-point exam and final exam together determines the final grade according to the method Cohen Schotanus (pass at 60% of the score of the best 5% of students after adjustment for guessing).

During and directly after the final exam, students have the opportunity to comment on questions or answers by a written request. The final answers are determined taking into account these comments and the psychometric analysis in accordance with the procedure of the national progression exam (“voortgangstoets”). The final answer key and an elucidation of adjusted or frequently missed questions will be published on Blackboard. After the examination a lecture will be organized where all questions that were marked by 5 or more students will be discussed.

Formative tests

This module contains a number of moments in which formative testing will occur (e.g. review lectures, work groups). These formative tests allow the student to assess whether the level of knowledge at that moment in the course is sufficient or not.
0.9 Study books

The module uses the following obligatory study books:
- *Oncologie*, vd Velde et al., 8th edition 2011
- *Clinical Medicine*, Kumar, Clark, 8th edition, 2012
- TRC section Pharmacotherapy

Below is a complete list, per book, of the pages that are considered exam material (in addition to other items mentioned under 0.7 Exam(s): material and matrix!). Within each week the pages to study for that week are precisely indicated in the reading lists per week. These lists also include the additional literature (which is not part of the exam material).

*Emery’s elements of medical genetics*, Turnpenny, 14th edition, 2011
Chapter 14, Cancer genetics, pages 209-232

Chapter 20, Cellular communities, Tissues, stem cells and cancer, pages 717-729 (starting with Cancer)

*Oncologie*, vd Velde et al., 8th edition 2011
Chapter 1, “Fundamentele aspecten van kanker”, pages 17-43
Chapter 2, “Klinisch genetische aspecten van kanker”, pages 45-57
Chapter 3B, “Epidemiologie van kanker”, pages 81-101
Chapter 4.6 “Tumormarkers”, pages 138-141
Chapter 6, “Chirurgisch oncologische behandelpincipes”, page 157-164
Chapter 7, “De rol van de radiotherapie bij de behandeling van kanker”, pages 165-174
Chapter 8, “Principes van de medicamenteuze antikanker behandeling”, pages 175-195
Chapter 16, “Tumoren van long, pleura en mediastinum tot en met 16.6 (trachea, pleura and mediastinum niet)”, pages 317-335
Chapter 17, “Oesofaguscarcinoom”, pages 345-354
Chapter 19, “Tumoren van lever, galwegen en pancreas, alleen 19.2.3 secundaire levertumoren, metastasen”, pages 364-366
Chapter 20, “Tumoren van de dunne en dikke darm, vanaf 20.2 (dunne darm niet)”, pages 375-387
Chapter 24, “Mammatumoren”, pages 431-451
Chapter 25, “Tumoren van de vrouwelijke geslachtsorganen”, pages 453-467 (upto 25.4)
Chapter 26, “Tumoren van de urinewegen, alleen 26.4 prostaatkanker”, pages 487-492
Chapter 36, “Behandeling van pijn en andere symptomen bij de patiënt met kanker”, pages 626-642

Foreign students will receive a list with corresponding pages from the study book *Clinical Medicine*, Kumar, Clark, 8th edition, 2012.
Robbins and Cotran Pathologic Basis of Disease, Kumar, Abbas & Fausto, 8th edition, 2009
Chapter 4, Hemostasis and Thrombosis, pages 115-125
Chapter 7, Alterations in Nonreceptor Tyrosine Kinases, pages 283-284 (till Transcription Factors) and Dysregulation of cancer-associated genes, pages 304-306 (till Gene Amplification)
Chapter 11, Atherosclerosis, pages 496-506
Chapter 13, Disorders of white cells, pages 592-607 (till Burkitt Lymphoma), Myeloid Neoplasms 629-624 (till Myelodysplastic Syndromes) and Chronic Myeloid Leukemia, pages 627-628
Chapter 14, Bleeding disorders, pages 666-674

Clinical Medicine, Kumar, Clark, 8th edition, 2012
Chapter 2, Stem cells, pages 33-34
Chapter 8, Introduction up to and including Acquired hemolytic anemia’s, pages 371-402 and Thrombosis, pages 414-429
Chapter 9, Hematological malignancies, The Leukemias, The Lymphomas, pages 451-467 (till Mantle cell lymphoma)
Chapter 14, Coronary artery disease, pages 723-740
Chapter 13, Peripheral vascular disease, pages 784-790

Article 1 and Attachment A are also part of the exam material.
Article 1: see link on Blackboard, DNA damage, repair and mutations, Harry Vrieling, pages 1-17
Attachment A: Leukemia and lymphomas, actualized by Prof.dr. J.H. Veelken and Dr. W.A.F. Marijt, July 2013

0.10 Relevant websites

- Blackboard: http://blackboard.leidenuniv.nl/
- COO 1-1: http://www.sanger.ac.uk/cosmic
- www.oncoline.nl
- www.iknl.nl
### 0.11 Week schedule

LT=lecture, RL=review lecture, PD= Patient demonstration, SSA= self-study assignment, COO=Computer assisted assignment, WG=work group, IS= Interactive session (half of the cohort)

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<td><strong>Week 1</strong></td>
<td>LT1-1</td>
<td>LT1-5</td>
<td><strong>WG1-1</strong></td>
<td><strong>Cancer and the genome</strong></td>
<td><strong>RL1-1</strong></td>
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<td><strong>SSA1-1 + COO</strong></td>
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<td><strong>PD2-1</strong></td>
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<td><strong>WG2-1</strong></td>
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<td>LT2-4</td>
<td>LT2-9</td>
<td><strong>IS2-1 and IS2-2</strong></td>
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<td><strong>Lymphoma</strong></td>
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<td><strong>SSA2-1</strong></td>
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<td>LT3-5</td>
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<td><strong>WG3-2</strong></td>
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<td><strong>Screening for cancer</strong></td>
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<td><strong>Midpoint exam</strong></td>
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<td><strong>Differences between cancers</strong></td>
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<td><strong>LT4-6</strong></td>
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<td>LT5-1</td>
<td><strong>PD5-1</strong></td>
<td><strong>WG5-1</strong></td>
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<td><strong>Week 6</strong></td>
<td>LT6-1</td>
<td><strong>RL6-1</strong></td>
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0.12 Teaching activities (study methods)

This module provides a great variety of teaching activities, each of which makes a significant contribution to the main learning objectives. It is, however, important to realize that self-study takes up the greater part of the scheduled time (60-70%), thus do not depend solely on the contact teaching activities!!

Lectures (LT and RL)
The module includes in total 49 lectures.
- Week 1: 9
- Week 2: 12
- Week 3: 9
- Week 4: 8
- Week 5: 8
- Week 6: 3
The titles of the lectures and contents in a nutshell are provided with the information per week.

Patient demonstrations (PD)
This module includes 6 patient demonstrations during the course, together illustrating both the palette of different cancer types and their clinical behavior and hematological.
N.B. These lectures will be in DUTCH.
- Week 1 PD 1-1, Lung Cancer (NSCLC)
- Week 2 PD 2-1, Hematological malignancy
- Week 3 PD 3-1, Breast cancer
- Week 4 PD 4-1, Colon cancer with metastatic liver disease
- PD 4-2, Metastatic breast cancer
- Week 5 PD 5-1, Allogenic stem cell transplantation and hematological malignancy

Self-study assignments (SSA)
The assignments for self-study are described with each week and require basic knowledge from previous modules. Each of the assignments specifically indicates what is expected of the student. The product of the self-study is what you have learned from the assignments. After the work group related to the self-study assignment the answers to this self-study assignment are placed on Blackboard, so that you can check your answers. However, effective learning requires that you first phrase your own answers before checking the answers!

Work groups (WG) and Interactive sessions (IS)
There are 6 work groups and 2 interactive sessions during this module. Work groups and interactive sessions are voluntary, but are strongly advised.
- Week 1: WG 1-1, Cancer and the genome
- Week 2: IS 2-1, Bleeding disorders
  IS 2-2, Thrombosis
  WG 2-1, Lymphoma
- Week 3: WG 3-1, Hereditary colorectal cancer
  WG 3-2, Screening
- Week 4: WG 4-1, Differences between cancers
- Week 5: WG 5-1, Gynecologic tumors (cervical and endometrial cancer)
**Multidisciplinary integrating lectures**
At the end of the course (Friday November 15th and Monday November 18th) there will be 6 case discussions. These case discussions are multidisciplinary integrating lectures in which the individual professionals are present in the lecture-room, sitting amongst the students. Multiple cases will be discussed interactively with the students and the professionals considering many aspects of the disease, including clinical presentation, diagnosis and treatment options. Each case will be presented in a power point presentation in which each following step can give rise to a discussion with the students. One of the goals of these lectures is to learn the students how professionals can and should interact with each other to reach the optimal treatment proposal for the individual patient.
N.B. These lectures will be in DUTCH.
- Case discussion Melanoma
- Case discussion Lymphoma
- Case discussion Metastatic prostate cancer
- Case discussion Paraneoplastic thrombotic events
- Case discussion Palliative and supportive care
- Case discussion Chemoradiation

**E-learning**
COO in week 1
TRC Pharmacology

**0.13 TRC Pharmacology**

**Introduction**
In this module your basic knowledge of pharmacology will be broadened by drugs with indications in oncology and hematology. The core medication list (see Blackboard) serves as basis for the mechanisms of drug action that need to be applied in patient cases where pharmacotherapeutics is relevant. Most of the pharmacology and therapeutics knowledge is integrated in the lectures of this module.

**Objectives**
You know the following items for each drug:
1. the classification of the drug
2. the mechanism of action
3. the most important indications
4. the most relevant side effects

**Learning materials**
- TRC Pharmacology Database (access via Blackboard)
  Chapter Oncology: “Treatment of tumors” and “Palliative therapy”
  Chapter Hematology: “Thrombosis”
- Farmacotherapeutisch Kompas or British National Formulary (BNF)

Recommended literature (for more details)
- *The Pharmacological Basis of Therapeutics*, Goodman and Gillman, 12th edition
Overview
Following reading is essential for your progress in pharmacology and therapeutics:
1 Introduction of farmacotherapeutisch kompas, Geneesmiddelen, Bloed, Middelen bij trombose, AND Geneesmiddelen, Middelen bij maligne aandoeningen
2 Self-study of TRC Pharmacology Oncology and Hematology
3 Self-study of side effects in the Kompas or BNF
4 Self-study assignment TRC, study core medication list
5 All information and links are accessible via Blackboard.

0.14 English and Dutch in the module

The module will be attended by a number of non-Dutch speaking foreign students. Therefore the following arrangements have been made:
- Most of the lectures and slides will be in English.
- The patient sessions and the multidisciplinary integrating lectures however will be in Dutch!
- One work group will be in English.

The exam will be both in Dutch and English. Questions and answers for each question will be provided in both languages. Answers to ‘open-end’ questions may be written in Dutch.

0.15 Pedigree Family Dekker

In year 1, in the module “Van Start tot Arts” the family Dekker was introduced during the work groups (Luuk Dekker†, Stijn Dekker, Indira (Almir), Chantal Dekker, Dennis Dekker and Mitchell Dekker). Mitchell is married with Marloes. They have two kids Robin and Anne. The names of the family members, used in the module of the first year are indicated in bold. In this module some (new) family members of the Dekker family will be introduced in the work groups and SSAs. As you can observe the pedigree is quite extensive. The medical histories of the known family members in the module book “Van Start tot Arts” are still relevant and should be used in the new cases.
3. Luuk Dekker† 17. Theo vd Berg 31. Harry Dekker
4. Roos van der Steen 18. Froukje vd Berg 32. Bas Schoen
6. Ans Hanen† 20. Theo vd Laan 34. Alex Schoen
13. Judith Dekker 27. Marloes Aarts
0.16 The ‘rules of the game’

Contact
IMPORTANT: For questions please email to the secretary Mrs. M. Veelenturf and NOT directly to the module coordinators.

Lectures
Please come in time. If you arrive late, please take the high entrance and do not disturb the lecture. Professional behavior of students includes a listening attitude and refraining from unsolicited talking during lectures. The teacher may cancel the lecture if too much talking precludes good teaching. All lectures will be placed on Blackboard afterwards.

Patient demonstrations/sessions
NOTE: Patient demonstrations are in Dutch. Late arrivals are NOT allowed during a patient demonstration. Professional behavior of students dictates that you discuss patients only with your colleague students if this cannot be overheard by others. Patient demonstrations will not be placed on Blackboard.

Work groups
Work groups are voluntary but are advised. With each week in the module book the required preparations for the corresponding work group are indicated. Students are expected to prepare for the work group and participate actively!! The work group tutors will make notes if students do not fulfill these requirements and these will be made available to the coordinator of the line professional education. Be present on the indicated hour. The teacher may refuse your entry if you arrive more than 10 minutes late.

Exam
Students have the opportunity to sign up for both the mid-point and the final exam until 10 working days before the exam (thus October 23rd, 23.59 and November 11th, 23.59 respectively) exactly. Students can and should check their sign up via uSis (deelhistorie student) whether they are on the list. After the closure time, the list with registered students will be published on Blackboard. Students who are not on the Blackboard list while the enrollment is listed in uSis ‘deelhistorie student’ must bring a printout of the ‘deelhistorie’ to the exam as proof of registration!! Students who are not on the list AND do not have a printed proof of registration are NOT allowed to do the exam and will be sent away. It is possible to sign off for the exam until 10 working days before the exam (thus October 23rd, 23.59 and November 11th, 23.59) exactly. If after that time point unforeseen circumstances arise that prohibit doing the exam, the student must notify DOO and provide an explanation.

During both mid-point and final exam the use of books, notes, internet or mobile phone is NOT allowed and these have to be stored and switched off.

The rules for release of blocked exam marks, as indicated by DOO, will be followed strictly.
1. Week 1

1.1 Introduction

Cancer is one of the most common and severe diseases affecting in some form or another approximately one third of the population in the Western world and is responsible for about 20% of all deaths. During this week, you will be acquainted with the kinds of genes that have been implicated in cancer development, the cellular processes that become affected and the (mutational) mechanisms that cause cancer genes to dysfunction. Moreover you will learn both the nomenclature of malignant tumors and the pathological and clinical differences between benign and malignant tumors. Furthermore you will understand how the morphological cellular and tissue changes are reflected by the genomic changes. Special attention will be given to the cellular processes that govern genome stability and so protect the genome against DNA damage and the induction of unwanted mutations. Furthermore, we will discuss the impact of recently developed technologies that allow (full) genome scanning of tumors on the identification of culprit mutational events and the possibilities this offers for cancer diagnosis and therapy.

1.2 Week schedule

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<td>SSA1-1 + COO</td>
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<td><strong>WG1-1</strong> Cancer and the genome</td>
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</table>

1.3 Subthemes addressed during this week

From the list of themes and subthemes on page 9 the subthemes that will be addressed during this first week are:

1. The etiology of malignancies
   a. Genetics and epigenetics
   b. Cancer biology
   c. Hereditary cancers
2. Nomenclature, staging principles and basics in treatment modalities and decisions of malignancies
   a. Nomenclature
   b. Diagnostic procedures and staging principles
3. Clinical and pathological aspects of the most frequent types of malignancies
   a. Non-small cell lung cancer
4. Clinical and pathological aspects of hematological malignancies
   a. Hematopoiesis
1.4 Activities

- Study the pages indicated in the reading list below before the lectures
- Follow the lectures (LT 1-1 – LT`1-9)
- Perform the SSA 1-1 and COO 1-1 below before work group WG 1-1 on Thursday
- Prepare for and participate actively in WG1-1
- Prepare for RL 1-1 and attend PD 1-1

1.5 Reading list

- *Emery’s elements of medical genetics*, 14th edition:
  Chapter 14, Cancer genetics, pages 209-232
- *Essential cell biology*, 3rd edition:
  Chapter 20, Cellular communities, Tissues, stem cells and cancer, pages 717-729 (starting with Cancer)
- “*Oncologie*”, 8th edition
  Chapter 16, “Tumoren van long, pleura en mediastinum tot en met 16.6 (trachea, pleura and mediastinum niet)”, pages 317-335
- Article 1: see link on Blackboard
  *DNA damage, repair and mutations*, Harry Vrieling, pages 1-17

Additional literature:
- *Robbins and Cotran Pathologic basis of disease*, 8th edition:
  Chapter 7, Neoplasia, pages 259-330
- Article 2: see link on Blackboard
  *Hallmarks of Cancer. The next generation*, Hanahan and Weinberg, Cell 144, pages 646-674
- Article 3: see link on Blackboard
  *Exploring the Genomes of Cancer Cells: Progress and Promise*, Stratton, Science Vol 331, pages 1553-1558

Additional website:
- [http://www.sanger.ac.uk/cosmic](http://www.sanger.ac.uk/cosmic)

1.6 Lectures, patient demonstration and review

- LT 1-1: Opening lecture and Introduction to the course
- LT 1-2: Cancer biology. This lecture will provide an overview of the genetic and molecular changes that are required to transform a normal cell into a cancer cell.
- LT 1-3: Genome integrity. In this lecture the various cellular defense mechanisms that have evolved to preserve the integrity of the genomes of our cells will be discussed.
- LT 1-4: Cancer genomes. This lecture will focus on the current status of the various types of genomic analyses that are performed to molecularly dissect the pathways involved in cancer development.
- LT 1-5: Normal hematopoiesis. This lecture will focus on the mechanism of differentiation of stem cells to highly differentiated end-stage cells and the regulation of this process by cytokines/growth factors and their receptors and the physiological response on endo- and exogenous factors.
- LT 1-6: General principles: cancer development. In this lecture insight will be provided into the relation between genetic alterations in cells and morphological changes in the affected cells and tissues.
- LT 1-7: General principles: nomenclature, grading and staging. In this lecture the classification and nomenclature of benign and malignant tumors will be discussed. Moreover, the tumor cell characteristics that are used to classify a tumor as malignant will be described. Finally, attention will be paid to tumor grading and tumor staging.
- LT 1-8: General principles: metastasis. This lecture concentrates on the mechanisms and routes of cancer cell dissemination (metastasis).
- LT 1-9: Lung cancer (NSCLC). In this lecture the clinical and pathological aspects regarding NSCLC including diagnosis and treatment options will be discussed.
- RL 1-1: Review Cancer and the genome: During this plenary session some examples of exam questions will be discussed and you will have the opportunity to ask any remaining questions about this topic.
- PD 1-1: Patient demonstration: In this lecture a patient with non-small cell lung carcinoma will be interviewed. Besides the clinical information regarding diagnosis, staging procedures and treatment options students will see the impact of having/getting the diagnosis of cancer on your whole life.

1.7 COO 1-1

Perform this COO before attending the work group on Thursday (WG 1-1 Cancer and the genome).

The identification of genes that are mutated and hence drive oncogenesis has been a central aim of cancer research since the advent of recombinant DNA technology. The Cancer Genome Project is using the human genome sequence and high throughput mutation detection techniques to identify somatically acquired sequence variants/mutations and hence identify genes critical in the development of human cancers. This initiative will ultimately provide the paradigm for the detection of germ line mutations in non-neoplastic human genetic diseases through genome-wide mutation detection approaches. The COSMIC database (Catalogue of Somatic Mutations in Cancer) is designed to store and display somatic mutation information and related details and contains information relating to human cancers. Use for answering the questions and assignments below information available at the COSMIC database website [http://www.sanger.ac.uk/cosmic](http://www.sanger.ac.uk/cosmic).

Go to the homepage and search the database for mutations in a specific gene (e.g. TP53). Search results will provide many links with the most relevant being on top. After selecting the top search result a schematic overview of the gene is presented. By clicking ‘distribution’ in the right-hand panel you obtain information on the type of mutations (mutational spectrum) found in tumors. Subsequent selection of ‘histogram’ provides more details on the mutational spectrum (e.g. the distribution of various types of mutations over the gene).

Since in not all studies the complete gene was sequenced, mutations in a particular (more frequently analyzed) region of a gene may be overrepresented. To get a more unbiased overview of all mutations found in a gene select ‘from systematic screen’ from the option ‘systematic screen’ in the right hand panel. Choosing these options for the genes TP53 and KRAS will provide you with pictures similar as the Screen dumps of TP53 and KRAS which can be found on Blackboard.
1. Reason on the findings for the TP53 gene whether it is most probably a tumor suppressor gene (TSG) or an oncogene. Do the same for KRAS.

2. Investigate for BRAF, APC, IDH1, PTEN and EGFR the mutational spectra in the COSMIC database and reason for each gene whether it is most likely a TSG or an oncogene.

3. Various hotspots for amino acid changes are present in the mutational spectrum of TP53, e.g. amino acids 248 and 273. Give three plausible explanations for the presence of mutational hotspots.

4. From the mutational spectrum of EGFR it is apparent that apart from a very frequent highly specific base pair change in exon 21 that causes an amino acid alteration (L858R), also small deletions/insertions are being found in particular in the area of amino acids 746-750.
   a. Do these deletions/insertions alter the reading frame?
   b. Does this finding comply with your reasoning whether EGFR is a TSG or an oncogene?

5. Explain why for the development of anti-cancer drugs efforts are more frequently focused on targeting tumor cells carrying a particular mutated oncogene than a mutated TSG.

6. Suppose that you would like to develop an anti-cancer drug against an activated oncogene. Discuss two criteria of the mutational spectrum of that particular oncogene that beforehand should enhance the chance on general applicability of the drug and treatment success. Are there any other demands concerning the specificity of the drug that should be fulfilled?

1.8 SSA 1-1

Perform this SSA 1-1 before attending the work group on Thursday (WG 1-1 Cancer and the genome)

[see pedigree below] The 27 year old son Tjeerd of Huub Dekker has been diagnosed with nevoid basal cell carcinoma syndrome (NBCCS) because of macrocephaly, facial milia and multiple basal skin cancers. NBCCS is transmitted as an autosomal dominant trait. The PTCH gene that is responsible for this disorder is located on chromosome 9. Molecular analysis of tumor and non-tumor DNA from an affected individual reveals heterozygosity of the gene in the patient’s blood cells but absence of one allele in the tumor. What does this imply about the mechanism of action of the responsible gene regarding tumor formation? If the disorder was inherited from the father of the patient referred to here, would you predict that the allele lost in the tumor would be the one inherited from the mother or father?
2 Highly specific chromosome translocations have been shown to be responsible for the onset of certain types of lymphomas and leukemias since they result in the activation of a particular oncogene. Examples include translocations between chromosomes 8 and 14 in patients with Burkitt's lymphoma and between chromosomes 9 and 22 in patients with chronic myelogenous leukemia (CML). Discuss the two main mechanisms by which a chromosome translocation can activate a proto-oncogene? Is it possible that a translocation could inactivate a tumor suppressor gene?

3 Some years ago, knockout mice were generated in which the \textit{TP53} tumor suppressor gene had been deleted. The figure below is a graphical presentation of the occurrence of spontaneous tumors in mice with three different genetic backgrounds: \(+/+\) = wild type mouse; \(+/-\) = heterozygous for loss of \textit{TP53}; \(-/-\) = homozygous for loss of \textit{TP53}.

\begin{itemize}
  \item [a] What do you conclude from the results shown?
  \item [b] How will the curves shown in the figure below change if the mice were exposed to a mutagenic dose of ultraviolet light on a daily basis. Indicate what you expect to happen with the curves in this figure.
\end{itemize}

\begin{figure}[h]
  \centering
  \includegraphics[width=0.5\textwidth]{tumor_curves.png}
  \caption{Graphical presentation of spontaneous tumor occurrence in knockout mice.}
\end{figure}

4 \textit{TP53} plays a central role in the regulation of the cell cycle. Other tumor suppressor genes such as \textit{RB} and \textit{CDKN2A} (\textit{p16\textsuperscript{Ink4A}}) also have roles in cell cycle control. In contrast to the wide spectrum of tumors found in patients with a germ line mutation in \textit{TP53}, the type of tumors occurring in patients with a mutation in \textit{RB} or \textit{CDKN2A} (\textit{p16\textsuperscript{Ink4A}}) are quite tissue specific (\textit{RB} mutation: retinoblastoma, osteosarcoma; \textit{CDKN2A} (\textit{p16\textsuperscript{Ink4A}}) mutation: melanoma). Provide a reason for this variation in tumor tissue specificity.

5 \textit{TP53} is an averagely sized gene and does not become more frequently mutated than comparable genes. Although more than 50\% of tumors contain mutations in the \textit{TP53} gene, disruption of the p53 pathway is found in over 90\% of all tumors. An example of an alternative route leading to p53 dysfunction is the over-expression of the \textit{MDM2} gene, which is involved in the degradation of p53 protein after completion of repair. Explain why disruption of the p53 pathway is so important in cancer development.
6 A large proportion of the hereditary cancer syndromes have a defect in a genome maintenance pathway such as DNA repair. Discuss why such a defect will strongly increase the chance for an individual to develop cancer. Give examples of three agents to which you are exposed on a daily basis that can cause DNA damage and that therefore may enhance cancer development.

7 Mutations can be subdivided into different classes such as a) frameshifts, b) basepair substitutions, c) chromosomal translocations and d) intragenic deletions. Compare these different classes of mutations on their ability to cause phenotypic effects.

8 Mammalian cells repair various types of DNA damage with higher efficiency from actively transcribed genes. Why can it be beneficial for a cell to preferentially repair active genes? How is preferential repair of active genes organized? Is this type of repair relatively more important for rapidly dividing or for non-dividing cells?

9 The chemical structure of the pyrimidine bases in DNA and RNA are highly similar. What base is formed when cytosine becomes deaminated? If uncorrected, to what type of mutation will deamination of cytosine in DNA most likely lead?

10 Consider the following reactive properties of some chemical compounds. Based on this characteristic which of these compounds do you expect to be most mutagenic at equal DNA lesion frequencies?
   a One that depurinates DNA.
   b One that produces single strand nicks into the sugar-phosphate backbone of DNA.
   c One that causes thymidine dimers.
   d One that crosslinks together the two strands of the double helix.

11 [see pedigree below] Tjeerd’s 18 year old sister Lia received standard induction chemotherapy for acute lymphoblastic leukemia followed by standard dose cranial radiation prophylaxis (18 Gy). Severe chemosensitivity and acute radiation reactions occurred and unfortunately she died after 8 months from late radiation damage. Genetic analysis identified the girl to be a carrier of a homozygous mutation in the gene encoding DNA ligase IV. From the information above elude in which DNA repair pathway DNA ligase IV will play a critical role.
Xeroderma pigmentosum, which is commonly known as XP, is an inherited condition characterized by an extreme sensitivity to ultraviolet (UV) rays from sunlight. This condition mostly affects the eyes and areas of skin exposed to the sun. Some affected individuals also have problems involving the nervous system. In addition, XP patients have a highly elevated risk for the development of skin cancer in sun-exposed areas of their body. Homozygous mutations in seven distinct genes have been identified to cause the XP phenotype. Explain how a single phenotype can associate with mutations in multiple genes.

Frequent and extensive exposure to solar UV light strongly enhances the risk for developing basal and squamous cell carcinomas. Below the various steps involved in skin cancer induction are depicted. Correctly combine the pictures with the provided concepts in the scheme below:

1.9 Work group WG 1-1, Cancer and the genome

The content of this work group will be placed on Blackboard shortly prior to the beginning of the work group. The questions of this work group will be discussed at the end of the work group.
2. Week 2

2.1 Introduction

During this week the focus will be on the mechanism of hemodynamic disorders (hemostasis, atherosclerosis and thrombosis) and on hematological malignancies. Moreover the basic principles of cancer treatment (surgery, radiation and systemic) are explained.

Hemostasis is the process that maintains blood in a clot-free state under physiological circumstances and prevents excessive blood loss upon vascular injury. When vascular injury occurs, the vessel constricts, platelets aggregate and form a platelet plug, and proteins of the procoagulant system will stabilize the clot via a dense fibrin network, while proteins of the anticoagulant and fibrinolytic systems prevent uncontrolled clot formation. This balance between procoagulant, anticoagulant and fibrinolytic factors has to be tightly regulated to ensure rapid and localized clot formation, and disturbance of this balance can lead to either a hypocoagulable or hypercoagulable state, which can subsequently result in bleeding or thrombosis, respectively. Thrombus formation can occur in both the arterial and venous system. Within this module we will discuss the basic mechanisms of disease in the development of arterial and venous thrombosis. Hereditary and acquired risk conditions for venous thrombosis will be discussed, including the relation of venous thrombosis and cancer. Arterial thrombosis as a result of atherosclerotic rupture is part of the curriculum as well.

In the field of hemato-oncology the knowledge of tumor cells is relatively advanced. This applies to such aspects as: oncogenesis, stem cell concept, cell kinetics, differentiation and maturation, spread and homing, sensitivity to radiation and chemotherapy, the development of resistance and the occurrence of secondary tumors. Many of these fundamental aspects can be directly related to the clinical behavior in the patient. There is also an increasing number of therapeutic possibilities that are partly based on the specific biological properties of tumor cells.

2.2 Week schedule

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<thead>
<tr>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
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<td>LT2-7</td>
<td>LT2-10</td>
<td>LT2-12</td>
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<td></td>
<td>LT2-3</td>
<td>LT2-8</td>
<td>IS2-1 and IS2-2</td>
<td>WG2-1</td>
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<td></td>
<td>LT2-4</td>
<td>LT2-9</td>
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<td>Lymphoma</td>
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<td>LT2-5</td>
<td>SSA2-1</td>
<td>SSA2-2</td>
<td></td>
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</tbody>
</table>

2.3 Subthemes addressed during this week

From the list of themes and subthemes on page 9 the subthemes that will be addressed during this week are:

2. Nomenclature, staging principles and basics in treatment modalities and decisions of malignancies
   b. Diagnostic procedures and staging principles
   c. Basic treatment modalities and decisions
d Heterogeneity in cancer behavior

3 Clinical and pathological aspects of the most frequent types of malignancies
   a Breast cancer
   b Colorectal cancer
   d Prostatic cancer

4 Clinical and pathological aspects of hematological malignancies
   a Hematopoiesis
   b Leukemia
   c Lymphoma

Mechanism of disease: Hemodynamic disorders

6 Thrombosis and Atherosclerosis
   a Hemostasis
   b Thrombosis
   c Atherosclerosis

2.4 Activities

- Study the pages indicated in the reading list below before the lectures
- Follow the lectures (LT 2-1 – LT 2-12)
- Perform SSA 2-1 below before the “Interactive sessions” IS 2-1 and IS 2-2
- Prepare for and participate actively during IS 2-1 and IS 2-2
- Perform SSA 2-2 below before attending work group WG 2-1
- Prepare for and participate actively in WG 2-1
- Attend PD 2-1

2.5 Reading list

- Robbins and Cotran Pathologic basis of disease, 8th edition:
  Chapter 4, Hemostasis and Thrombosis, pages 115-125
  Chapter 7, Alterations in Nonreceptor Tyrosine Kinases, pages 283-284 (till Transcription Factors) and Dysregulation of cancer-associated genes, pages 304-306 (till Gene Amplification)
  Chapter 11, Atherosclerosis, pages 496-506
  Chapter 13, Disorders of white cells, pages 592-607 (till Burkitt Lymphoma), Myeloid Neoplasms 629-624 (till Myelodysplastic Syndromes) and Chronic Myeloid Leukemia, pages 627-628
  Chapter 14, Bleeding disorders, pages 666-674

- Clinical Medicine, 8th edition
  Chapter 2, Stem cells, pages 33-34
  Chapter 8, Introduction up to and including Acquired hemolytic anemia’s, pages 371-402 and Thrombosis, pages 414-429
  Chapter 9, Hematological malignancies, The Leukemias, The Lymphomas, pages 451-467 (till Mantle cell lymphoma)
  Chapter 14, Coronary artery disease, pages 723-740
  Chapter 13, Peripheral vascular disease, pages 784-790
2.6 Lectures and patient demonstration

- LT 2-1: Framework oncology – points to consider. In this lecture basic concepts in oncologic thinking, consisting of a step-wise approach when treating a new cancer patient, are discussed.
- LT 2-2: Surgical oncology. This lecture will focus on basic concepts and terminology in surgical oncology.
- LT 2-3: Radiation oncology. In this lecture an introduction to radiation oncology is given including technical issues and toxicity.
- LT 2-4: Medical oncology. This lecture focusses on basic concepts in systemic treatment, chemotherapy vs hormonal therapy vs targeted agents, biologicals, and possible treatment schedules.
- LT 2-5: Chemoradiation. In this lecture the concepts behind chemoradiations are discussed, including radiosensitizers, therapeutic windows and commonly used combination regimens. Several clinical cases will be given as examples.
- LT 2-6 and LT 2-7: Primary hemostasis. In these 2 lectures thrombosis is introduced, and primary hemostasis and related aspects are explained.
- LT 2-8 and LT 2-9: Secondary hemostasis. In these 2 lectures secondary hemostasis is introduced. Acquired and hereditary risk factors of venous thrombosis and underlying mechanisms are explained.
- LT 2-10: Atherosclerosis. In this lecture the mechanisms underlying atherosclerosis development and arterial thrombosis are explained.
- LT 2-11: Anemia, leukemia. This lecture will focus on the etiology of increased or decreased production of blood cells, the principles of diagnosis and the diagnostic tools.
- LT 2-12: CML, genetic background. This lecture will focus on the development of chronic and acute myeloid malignancies, the diagnostic process and treatment possibilities.
- PD 2-1: Patient demonstration Leukemia. In this lecture a patient with leukemia will be interviewed and the clinical and pathological aspects of the disease will be discussed.
2.7 SSA 2-1

During Wednesdays lectures (LT 2-5 – LT 2-9) the following important concepts were discussed.
- Trouseau sign: Thrombosis in relation to cancer
- Structure and function of the vessel wall and endothelium. Importance to hemostasis and cancer
- Primary hemostasis, vessel wall injury, platelet adhesion and aggregation, von Willebrand factor
- Therapeutic interventions: mechanisms of action of platelet aggregation inhibitors (aspirin, clopidogrel)
- Secondary hemostasis, proenzymes, enzymes, cofactors, coagulation cascade, vitamin K, (acquired) hemophilia
- Anticoagulant factors, protein C/S, antitrombin, factor V Leiden, protrombin G20210A
- Risk factors for venous thrombosis (acquired and hereditary) with a focus on cancer as a risk factor for venous thrombosis
- The role of coagulation factors and tissue factor in the development of cancer
- Therapeutic interventions: mechanisms of action of vitamin K antagonists (acenocoumarol, fenprocoumon), heparin/LMWH, novel oral anticoagulants (NOACs)
- Atherosclerotic plaque development the role of cholesterol
- Atherosclerotic plaque rupture and arterial thrombosis
- Therapeutic interventions: platelet aggregation inhibitors, thrombolysis by fibrinolytic drugs

SSA 2-1 serves as a preparation for the two Interactive sessions ‘Hemostasis and Thrombosis’ (IS 2-1 and IS 2-2). You will train with the concepts discussed during the lectures. Concepts will be discussed again during the seminars.

Answer the questions below.

Cancer and thrombosis
1 Patients with cancer have an increased risk of developing venous thrombosis. What is the relative risk of cancer for developing venous thrombosis? Is this the same for all types and stages of cancer?
2 Patients with venous thrombosis are at risk for developing cancer in the (near) future. How big is this risk? Is the cancer risk depending on the type of thrombosis?
3 Should patients with venous thrombosis be screened for the presence of malignancy?
4 Should the thrombosis in cancer patients be treated differently? Is the cancer influenced by the anticoagulant treatment?
5 What is the role of tissue factor in the development of cancer?

Primary hemostasis
6 Which platelet receptors play a role in platelet adhesion? What are the ligands for those receptors?
7 Which platelet receptors play a role in platelet activation and aggregation? What are the ligands for those receptors?
8 Which two type of granules are exocytosed upon activation of platelets? What are their respective contents?
9 What is the working mechanism of aspirin, clopidogrel, and abciximab?
Secondary hemostasis
10 Which pro-enzymes and pro-cofactors play a role in the coagulation cascade?
11 What is the difference between the enzymes and cofactors?
12 What are the differences between the ‘extrinsic’ and ‘intrinsic’ pathways of coagulation? Which route is clinically most important?
13 Which anticoagulant proteins are involved in the inhibition of coagulation? Which enzymes and/or cofactors are inactivated by these anticoagulant proteins and how?

Fibrinolysis
14 Which two components of the fibrinolytic pathway enhance fibrinolysis and which two components inhibit fibrinolysis?
15 What is the mechanism of action of TAFI?

Coagulation assays
16 Explain why vitamin K deficiency leads to a prolongation of the prothrombin time (PT) as well as the activated partial thromboplastin time (APTT)?
17 What is the effect of factor VIII deficiency on the PT and APTT?
18 Which coagulation factor deficiency leads to a prolonged PT, but does not influence the APTT?

The thrombo-hemorrhagic balance
19 Do the following conditions lead to bleeding or thrombosis? If applicable, what is the name of the respective disease?

<table>
<thead>
<tr>
<th>Clinical symptom: bleeding or thrombosis?</th>
<th>Which disease?</th>
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<tbody>
<tr>
<td>Factor VIII deficiency</td>
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<tr>
<td>Increase in number of platelets</td>
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<tr>
<td>Excess of plasminogen</td>
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<td>Factor IX deficiency</td>
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<td>Defect Glycoprotein Ib receptor (GPIb)</td>
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<tr>
<td>Dysfunctional von Willebrand factor</td>
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<td>Factor Va insensitive to inactivation by activated protein C</td>
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<tr>
<td>Low level of antithrombin</td>
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<td>Deficiency of ADAMTS13</td>
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<tr>
<td>Use of aspirin</td>
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</table>
Venous thrombosis: risk factors, diagnosis and treatment

20 Which hereditary risk factors of venous thrombosis are presently known? Subdivide these into “gain of function” and “loss of function” mutations.

21 Factor V Leiden refers to a mutation in the Factor V gene. a) Which mutation is this? b) What are the consequences at the amino acid level? c) Which step in the Factor V life cycle is affected? d) Which other coagulation factor plays a major role in this step?

22 How does the G20210A mutation in the prothrombin gene lead to an increased risk of venous thrombosis?

23 What are the clinical symptoms of venous thrombosis of the leg?

24 Which objective diagnostic tests are available for the diagnosis of deep vein thrombosis of the leg?

25 Which objective diagnostic tests are available for the diagnosis of pulmonary embolism?

26 What is the primary aim of treatment of venous thrombosis of the leg?

27 Which medications are used for the treatment of venous thrombosis and pulmonary embolism? In which sequence and for how long are these used.

Hereditary bleeding disorders

28 What is the difference between mild, moderate and severe hemophilia?

29 Which medications are available for the treatment of hemophilia A and B, respectively?

30 What is the difference between type 1 and type 2 von Willebrand disease?

31 In which way do the bleeding symptoms of hemophilia and von Willebrand disease differ?

2.8 Interactive sessions IS 2-1 and IS 2-2

Interactive sessions IS 2-1 (Bleeding disorders) and IS 2-2 (Thrombosis) are interactive sessions for which you need to prepare in advance (by performing SSA 2-1). The cohort is divided into two groups (WG 1-12 and WG 13-24) and each group will follow both interactive sessions. The objects of discussion are:

IS 2-1, Bleeding disorders
Understanding the pathophysiology of coagulation on the basis of case presentations
Case presentations of patients suffering from:
- Acquired hemophilia
- Hemophilia A and B
- Von Willebrand’s disease
- Thrombocytopenia and diffuse intravascular coagulation in cancer

IS 2-2, Thrombosis
- Clinical aspects, diagnosis and treatment of thrombosis
- Impact cancer on diagnosis and treatment
- Prognosis in cancer and thrombosis
- Case presentation arterial thrombosis
In order to prepare yourself for the work group Lymphomas that shall deal with the pathogenesis, diagnosis and treatment of lymphomas you are required to study the following texts.

- Clinical Medicine, 8th edition: Chapter 9, pages 456-467 (till Mantle cell lymphoma).
- Robbins and Cotran Pathologic Basis of Disease, 8th edition, Chapter 13, Disorders of white cells, pages 592-607 (till Burkitt Lymphoma).
- Text by Professor Veelken on the pathogenesis of lymphomas (will be available on Blackboard).

Prior to the start of the work group you will have to hand in a summary of the texts in which all aspects regarding pathogenesis, symptoms, diagnosis, prognosis, and treatment of CLL, HL, and NHL are addressed. Try to create a conceptual framework to deal with these aspects.

2.10 Work group WG 2-1, Lymphoma

During this work group you will be given an assignment with several case studies which you will prepare and discuss. The work group will be led by a process supporter and the questions are answered by the students in as much detail as possible. The role of the instructors is only supportive.
3. Week 3

3.1 Introduction

During this week the emphasis will be on solid tumors. Breast cancer and colorectal cancer serve as examples to explain the mechanism of development of solid tumors. Diagnostic procedures and treatment decisions will be discussed based on the “Framework oncology” mentioned last week. Although each cancer patient will be treated by one physician you should be aware of the fact that cancer requires a multidisciplinary approach in which an optimal treatment plan is made for the patient. Attention will be given to the organization of cancer care in the Netherlands, a rapidly changing field with many players! Screening for cancer with its pros and cons will be discussed at the end of this week.

3.2 Week schedule

<table>
<thead>
<tr>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
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<tbody>
<tr>
<td>LT3-1</td>
<td>Line day</td>
<td>LT3-5</td>
<td>WG3-1 Hereditary</td>
<td>WG3-2 Screening</td>
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3.3 Subthemes addressed during this week

From the list of themes and subthemes on page 9 the subthemes that will be addressed during this week are:

1. The etiology of malignancies
   a. Genetics and epigenetics
   c. Hereditary cancers
   d. Environmental factors
2. Nomenclature, staging principles and basics in treatment modalities and decisions of malignancies
   a. Nomenclature
   b. Diagnostic procedures and staging principles
   c. Basic treatment modalities and decisions
   d. Heterogeneity in cancer behavior
   e. Palliative treatment
3. Clinical and pathological aspects of the most frequent types of malignancies
   a. Breast cancer
   b. Colorectal cancer
Psychosocial aspects of cancer, palliative and supportive care, organization of cancer healthcare and alternative medicine (quackery)

a. Complementary medicine
b. Cancer health care
c. Psychosocial aspects
d. Screening, counseling and follow-up

3.4 Activities

- Study the pages indicated in the reading list below before the lectures
- Follow the lectures (LT 3-1 – LT 3-9)
- Answer the questions of SSA 3-1 below
- Prepare, in advance, all assignments of WG 3-1 (short written answers)
- Answer the questions of SSA 3-2 below
- Read, in advance, the assignments of WG 3-2
- Prepare for and participate actively in WG 3-1 and WG 3-2
- Attend PD 3-1

3.5 Reading list

- Emery’s elements of medical genetics, 14th edition:
  Chapter 14, Cancer genetics, pages 209-232
- “Oncologie”, 8th edition
  Chapter 2, “Klinisch genetische aspecten van kanker”, pages 45-57
  Chapter 3B, “Epidemiologie van kanker”, pages 81-101
  Chapter 20, “Tumoren van de dunne en dikke darm, vanaf 20.2 (dunne darm niet)”, pages 375-387
  Chapter 24, “Mammatumoren”, pages 431-451

Additional literature:
- Article 4: see link on Blackboard
- Article 5: see link on Blackboard
- Article 6: see link on Blackboard

Additional website:
- www.iknl.nl
3.6 Lectures and patient demonstration

- LT 3-1: Breast cancer, basics. In this lecture basic clinicopathological, etiological and diagnostic aspects of breast cancer development are discussed.
- LT 3-2: Breast cancer, surgery and radiotherapy. This lecture will focus on the role of surgery and radiotherapy in breast cancer treatment.
- LT 3-3: Breast cancer, adjuvant treatment. In this lecture the role of adjuvant treatment options in breast cancer is discussed, including the use of prognostic and predictive factors in this clinical decision making and their pros and cons.
- LT 3-4: Clinical genetics. In this lecture clinical aspects of breast cancer are discussed in relation to the previous patient demonstration.
- LT 3-5: Cancer care organization in the Netherlands. During this lecture the focus will be on cancer care organization, including the discussion around volume and centralization and the role of the insurance-companies.
- LT 3-6: Debate on concentration in oncologic health care
- LT 3-7: Colorectal cancer, etiology and pathology. In this lecture the clinical, etiological, genetic, hereditary and pathological aspects of colon cancer are discussed
- LT 3-8: Colon cancer. Focus of attention during this lecture will be the surgical oncological aspects of colon cancer treatment.
- LT 3-9: Rectal cancer. This lecture concentrates on the surgical and oncological aspects of rectal cancer, including the role of neo-adjuvant (chemo)radiation.
- PD 3-1: Breast cancer, patient demonstration. A patient with early breast cancer is presented and the rationale of adjuvant therapy is discussed.

3.7 SSA 3-1

Answer all questions of this SSA. In doing so you will be guided through the study-material. In principle all answers can be found in the study books, specified in the reading list, and you should be able to find all answers yourselves. At the beginning of the work group you do have the opportunity to ask questions about this SSA.

Hereditary forms of cancer - general
1 The term ‘hereditary cancer’ is actually incorrect. Why?
2 How would you in practice explain to a patient with only a primary school education how cancer occurs?
3 What are the similarities and differences between sporadically occurring tumors and hereditary forms of cancer?
4 The cascade of genetic alterations that can lead to the development of tumors has been mapped the best in colon cancer. Which genes may be involved in the occurrence of colon cancer?
5 Which genes may contain a mutation in the germ line and what cancer syndrome is then the result?
6 The Law on Medical Treatment Agreement (WBGO, Wet op Geneeskundige Behandelingsovereenkomst) offers hospitals the opportunity to destroy medical data. Discuss why this may have disastrous consequences for patients and their families.
Colon cancer
7 With 13,000 new cases in the Netherlands every year (as of 2011), colon cancer is one of the most common tumors. What is the ‘lifetime risk’ for a Dutch man/woman?
8 What features would set us on the trail of a genetic predisposition?
9 In what percentage of intestinal tumors does genetic predisposition play an important role?
10 How can it be that sometimes different figures are given for this?
11 Early detection of colon cancer is crucial for successful treatment with a chance of cure. Make a list of the symptoms that occur with a tumor in the ascending colon and compare this with the symptomatology of a tumor in the sigmoid colon or rectum.

Breast Cancer
12 With 14,000 new cases in the Netherlands every year (as of 2011), breast cancer is the most common tumor in women. What features would set us on the trail of a genetic predisposition?
13 In what percentage of breast tumors does genetic predisposition play an important role?
14 [see pedigree, page 22] The 39 year old Els, daughter of the 65 year old Johan and 63-year old Lia feels a lump in the right breast.
   a What should be asked in the history? Indicate Els in the pedigree?
   b On what should particular attention be paid during the physical examination?
   c What further tests should be done if there is doubt that it is benign?
15 [see pedigree, page 22] The 34-year-old Marian, member of a dizygotic twin, says that two older sisters have had breast cancer. The eldest sister Judith twice, the first time on the left at the age of 36, the second time at the age of 40 in the other breast. The second sister Elvira had breast cancer at the age of 37. The mother died at age 50 from the consequences of cancer in the abdomen. A niece, the daughter of the 52 year old brother Kees of the mother, had breast cancer at the age of 32; a sister, Carla, of the mother is being treated for ovarian carcinoma.
   a Indicate the different family-members of the pedigree Dekker (page 22) and complete the pedigree with the additional information.
   b What is the likely diagnosis?
   c What data are needed to confirm this suspicion?
   d What tests should be done and who will be examined first?
   e In what risk class is this woman without any further investigation?
16 A 38-year-old woman has breast cancer. She says that her mother died of breast cancer at the age of 44. She says her brother had breast cancer at the age of 50.
   a Draw the family tree.
   b What is the likely diagnosis and what tests need to be done?
   c The woman has two daughters aged 8 and 6 years old. Are they eligible for examination?
   d Add them to the family tree.
   e What is your policy with regard to them, and why?

3.8 Work group WG 3-1, Hereditary colorectal cancer

All assignments for the work group colon cancer should be studied in advance. Please, prepare short written answers. In the work group the written answers will be discussed. In each work group a multidisciplinary approach is followed, a manner in which students will be trained in communication with a number of disciplines (General practitioner, Gastroenterologist/surgeon, Gynecologist, Pathologist and Clinical geneticist.
General practitioner
1. What do you do first when patients come to you with questions about colon cancer in the family?
2. Indicate in which cases you would make a referral and to what specialist: a) if the patient himself has symptoms and b) if the patient himself has no symptoms. Explain your answer.
3. What role can the GP have if, in one of his/her patients, a mutation is discovered which results in an increased risk of cancer?

Gastroenterologist/surgeon
1. In someone with a positive history for colon cancer you encounter resistance in the right lower abdomen. What do you do?
2. What is the differential diagnosis of a possible hereditary form of colon cancer? What are the starting age and the interval for periodic examination?
3. Is there a difference in treatment between patients that appear to have a sporadic form of cancer compared with patients with a hereditary predisposition?
4. Discuss the pros and cons of prophylactic colectomy.

Gynecologist
1. A 40-year-old female patient with excessive vaginal bleeding is referred. The family history is very suspicious in terms of a hereditary form of colon cancer. What do you do?
2. Suppose you find no abnormalities at all on physical examination; what is your policy then?
3. Is there a difference in treatment between patients that appear to have a sporadic form of cancer compared with patients with a hereditary predisposition?
4. Discuss the pros and cons of prophylactic hysterectomy.

Pathologist
1. You receive a resection for review: the ascending colon of a 36-year-old man with a large tumor. Briefly explain how you examine this tissue.
2. Which findings fit with a hereditary predisposition?
3. This tumor at a young age may have originated in the context of Lynch syndrome (HNPCC) by carrying a mutation in one of the ‘mismatch repair’ (MMR) genes. Describe a technique for demonstrating the suspicion of such a mutation in tissue material. Is such examination done routinely, or only on indication? If so, when?
4. With what technique can you examine what MMR gene is defective? What is the next step?

Clinical geneticist
1. A person requesting advice is referred with a family history that is very suspicious in terms of a hereditary form of colon cancer. He has no complaints at all. What additional testing do you do? What must you ask about the family?
2. In a man 25 years of age, more than a hundred polyps were observed scattered throughout the entire colon and of varying sizes.
   What should be asked about the patient and family?
   What is the diagnosis?
   What treatment should be carried out?
   What is usually the cause?
   What examination must therefore be done?
   Are family members eligible for examination? Explain your answer.
A 35-year-old woman tells us that her older brother had surgery at the age of 39 for colon cancer; an older sister had surgery for cancer in the uterus at age 42. Her father died at age 45 from the consequences of colon cancer and a brother of the father at the age of 40. Draw the family tree. What do you need to know in order to make a diagnosis? What is the most likely diagnosis? Does this family meet the Bethesda criteria? Explain your answer. The 35-year-old woman wishes to know what her chances of cancer are. What examination is needed in order to calculate her odds?

Describe the logistical course of affairs with suspicion of 1) Lynch syndrome and 2) FAP/MAP. What does the clinical geneticist do if a mutation is discovered in one of the patients that leads to a high chance of cancer?

Molecular geneticist
1. Make a list of the genes that are now studied with regard to hereditary colon cancer.
2. Blood is sent to your laboratory with the request to search for a mutation that leads to an increased risk of colon cancer. What information do you need to determine which gene should best be studied (first)?
3. Discuss with what type of mutations a link between tumor predisposition and mutations is (almost) certain and in what type of mutations this link is uncertain.
4. What resources does the molecular biologist have at his disposal if he discovers a deviation in the DNA in a colon cancer patient, to make a statement about the pathogenicity?

Psychologist
1. If a mutation is found in a family, it is certainly not so that every family member has himself examined. Discuss what motives and psychological mechanisms can play a role in this decision.
2. Discuss what role a psychologist can have with a person that wishes to be examined presymptomatically.
3. What role can the psychologist have if a mutation is found in one of the patients in the practice that leads to a high likelihood of cancer?
4. What role can the psychologist have regarding a favorable outcome of presymptomatic testing; in other words, can negative consequences also be associated with a favorable result?

3.9 SSA 3-2

Screening programs for cancer

To answer the questions below study the literature mentioned in the reading list.

Introduction
All medical care should seek to achieve at least one, preferably more, of the following goals: to relieve suffering, to prevent future suffering or to prolong life. Screening programs for cancer have mainly been developed to prevent future suffering or to avoid mortality due to the disease that was screened for. In the Netherlands screening programs to detect cervical cancer and breast cancer have been introduced in the past century, a screening program for colorectal cancer will start towards the end of 2013. There is debate about the usefulness of screening for prostate cancer and lung cancer.
Questions:
1. What is the incidence and mortality of breast cancer, cervical cancer, colorectal cancer, lung cancer and prostate cancer in the Netherlands (www.iknl.nl)
2. What is the age distribution of patients with cervical cancer and breast cancer? (www.iknl.nl)
3. Define the requirements for a good screening program for cancer.
4. Describe the definition of a false positive and a false negative test
5. Explain the term “interval cancer” with respect to a screening program?

Cervical cancer
All Dutch women aged between 35 and 60 years are invited for a screening test for cervical cancer every 5 years

Questions:
6. What are the early symptoms of cervical cancer?
7. Which test is used for the early detection of cervical cancer?
8. Which results of the PAP-smear do you know?
9. What is the follow-up after a positive PAP-smear?
10. What is the natural history of cervical cancer?
11. What is the primary treatment for cervical cancer?
12. Do you think that vaccination of 13-years old girls for HPV may be an alternative for cervical cancer screening in the future?

Breast cancer
Screening mammography for breast cancer was introduced in the Netherlands in 1990. All women aged between 50 and 75 years are invited biannually to undergo a mammography in one of the 64 regional buses. In 2009 911,441 underwent a mammography in this program and 1,9 % of the women were referred to a hospital for additional diagnostic. From the screened women 0,6 % appeared to have breast cancer, 70% of them had the disease at an early stage ( <stage 2)

Questions:
13. How is a mammography carried out?
14. Which complaints do women most frequently describe after they have undergone a mammography?
15. How is the result of a mammography described?
16. What is the follow-up of an abnormal mammography result of the screening?
17. Describe the BIRAD’s classification.
18. What is the initial treatment of early stage breast cancer?

The ten years survival after initial treatment for breast cancer in the Netherlands has increased from below 60 % in 1970 towards more than 80 % in 2013.

Questions:
19. Are there other potential explanations for the increase in overall survival for breast cancer other than screening programs?
20. What are the drawbacks for the screening program for breast cancer?
21. Define DCIS (ductal carcinoma in situ)
22. What is the treatment for DCIS?
Which costs are justified for the breast cancer program in the Netherlands? Take into account the total number of new breast cancer patients, the mortality and number of patients that are screened for breast cancer every year.

3.10 Work group WG 3-2, Screening for cancer

This work group is divided in 2 sessions.
- First session concerning breast cancer: half of the group prepares a power point presentation leading to the option that the breast cancer screening program in the Netherlands should be terminated. The other part of the group has to defend the opposite
- Second session concerning prostate cancer: half of the group prepares a power point presentation advocating the introduction of a screening program for prostate cancer starting at the age of 50, every year. The other part of the group defends the opposite
4. Week 4

4.1 Introduction

This week starts with a mid-point exam (one hour), for more information on this exam see page 15.

The emphasis in this week is on more ‘practical’ clinical issues like follow-up after initial treatment, usefulness of laboratory investigations to measure disease activity and treatment response, rare curative treatment options in metastatic disease and the differences in clinical behavior between cancer types and also between different patients with the same tumor. At the end of the week the frequent use by cancer patients of complementary medicine will be discussed.

4.2 Week schedule

<table>
<thead>
<tr>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
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<tbody>
<tr>
<td>Week 4</td>
<td>Midpoint exam</td>
<td>Line day</td>
<td>LT4-1</td>
<td>PD4-2</td>
</tr>
<tr>
<td>SSA4-1</td>
<td></td>
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<td>LT4-7</td>
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<tr>
<td>WG4-1</td>
<td></td>
<td>PD4-1</td>
<td>LT4-5</td>
<td>LT4-8</td>
</tr>
<tr>
<td>Differences between cancers</td>
<td></td>
<td>LT4-3</td>
<td>LT4-6</td>
<td></td>
</tr>
<tr>
<td>SSA4-2</td>
<td></td>
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</tbody>
</table>

4.3 Subthemes addressed during this week

From the list of themes and subthemes on page 9 the subthemes that will be addressed during this week are:

2. Nomenclature, staging principles and basics in treatment modalities and decisions of malignancies
   a. Diagnostic procedures and staging principles
   b. Basic treatment modalities and decisions
   c. Heterogeneity in cancer behavior
   d. Palliative treatment

3. Clinical and pathological aspects of the most frequent types of malignancies
   a. Breast cancer
   b. Colorectal cancer
   c. Prostatic cancer

5. Psychosocial aspects of cancer, palliative and supportive care, organization of cancer healthcare and alternative medicine (quackery)
   a. Complementary medicine
   b. Cancer health care
   c. Psychosocial aspects
4.4 Activities

- Study the pages indicated in the reading list below before the lectures
- Follow the lectures (LT 4-1 – LT 4-8)
- Perform the SSA 4-1 below
- Prepare for and participate actively in WG 4-1
- Attend PD 4-1

4.5 Reading list

- “Oncologie”, 8th edition:
  Chapter 4.6 “Tumormarkers”, pages 138-141
  Chapter 17, “Oesofaguscarcinoom”, pages 345-354
  Chapter 19, “Tumoren van lever, galwegen en pancreas, alleen 19.2.3 secundaire levertumoren, metastasen”, pages 364-366
  Chapter 26, “Tumoren van de urinewegen, alleen 26.4 prostaatkanker”, pages 487-492

Additional literature:
- “Oncologie”, 8th edition:
  Chapter 39, “Het gebruik van niet-reguliere behandelmijzen voor kanker naast de reguliere behandeling”, pages 667-675
- Article 7: see link on Blackboard

Additional website:
- [www.oncoline.nl](http://www.oncoline.nl)

4.6 Lectures and patient demonstrations

- LT 4-1: Follow-up after initial treatment for cancer. In this lecture we will discuss the pros and cons of follow-up schemes after initial cancer treatment including the current guidelines. Students will learn the differences between follow-up schemes in relation to locoregional recurrence and distant metastases and the differences of FU in relation to tumortype. Moreover the guideline "Herstel na Kanker" ([www.oncoline.nl](http://www.oncoline.nl)) will be discussed.
- LT 4-2: Debate on the usefulness of biomarkers in cancer patients. During this debate two cases (testistumor and ovarian cancer) will be used to illustrate the pros and cons of tumor biomarkers in diagnosis, evaluation of treatment and follow-up schemes
- LT 4-3: Colorectal cancer, treatment options liver metastasis. In this lecture the treatment options for liver metastasis will be discussed.
- LT 4-4: Heterogeneity in cancer. This lecture will focus on the biological heterogeneity of cancer behavior.
- LT 4-5 and LT 4-6: Tumor board locally advanced breast cancer. In these two lectures the multidisciplinary approach of two patients with cancer will be discussed. The first patient will be a locally advanced breast cancer patient. The other one concerns a young female with a rectal carcinoma and multiple (benign) polyps in the remaining colon.

- LT 4-7 and LT 4-8: Complementaire geneeskunde / alternatieve geneeswijzen. NOTE: These 2 lectures will be in DUTCH). In deze colleges zullen de alternatieve geneeswijzen die door sommige patiënten met kanker wordt gebruikt worden toegelicht. Naast een historisch overzicht over de verschillende behandelingen en de precieze definitie van alternatieve geneeswijzen zal er een debat worden georganiseerd tussen een voor- en tegenstander van gebruik van deze vormen van ‘therapie’ in de kankerbehandeling.

- PD 4-1: In this patient demonstration the clinic-pathological aspects of a patient with colorectal cancer will be presented and discussed.
- PD 4-2: In this patient demonstration a patient with a stage IV breast cancer, a so-called long survivor, will be presented and discussed.

4.7 SSA 4-1

As has been said before ‘cancer’ is a very heterogeneous group of diseases. Depending on the organ and tissue type involved the clinical behavior might vary enormously. Knowledge on this clinical behavior has been collected in the many centuries of the history of medicine. The effects of treatments applied (surgery, irradiation, chemotherapy) have been reported in (recent) medical literature.

Questions to be answered before a treatment can be proposed to a patient are:
- What is the nature of this tumor, the grade of differentiation, which organ is involved and has infiltration in surrounding tissue occurred? How is the latter question best assessed? What is the expected mode of spread for this tumor? What do we know of the incidence of spread at diagnosis? Should we, and if yes, how should we assess the extent of spread of the disease?
- What is the patients clinical condition? How does this affect the work-up of his cancer?
- What is the outcome of the staging procedures? Can the treatment intention still be: cure?
- What is the primary treatment option for this type of cancer? Surgery? (Chemo)Radiotherapy?

In work group WG 4-1 two very different types of cancer will be discussed. The differences involve prognosis, mode of spread, work-up and treatment options, all inter-related. By way of contrasting those types of cancer the relevance of knowledge of clinical behavior will be taught.

In preparation for work group WG 4-1 carefully study this “Framework oncology – points to consider”
Framework oncology - points to consider

You should consider the following questions when treating a new patient who has cancer:

1 **This patient has cancer, what does this mean for the patient?**
   Matters to consider could include comorbidity, their condition and treatment preferences.
   *If a patient does not want treatment, or if treatment is barely possible, an extensive examination does not make much sense.*

2 **What do I know about this type of cancer?**
   - Is it known to be particularly aggressive locally/continued growth?
   - Does it often create lymphogenic metastases?
   - Does it often create hematogenic metastases (in which organs)?
   - A combination of the two?
   *You need to think about this in terms of the staging. Are you going to stage? How extensively? Focused on which framework of questioning? Which method will you employ?*

3 **Primary treatment options?**
   *This is primarily determined by the organ of origin and the location of the tumor as well as the sensitivity to radiation and/or chemotherapy.*
   - Radiation therapy: Acute toxicology? Latent toxicology?
   - Chemotherapy / other systemic therapy: Side-effects? Stress on body?

4 **Consider adjuvant treatments?**
   - How great is the chance of a local recurrence? Does supplementary local treatment make sense? Radiation?
   - At this time, how great is the chance of metastasis / presence of micro-metastases at this time? Does supplementary systemic treatment make sense? Chemotherapy? Hormonal therapy? Targeted therapy?
   *When considering this question, the anticipated benefits of survival of the patient must play a role, weighed against the side-effects and stress of such a treatment. At the macro level, the 'numbers needed to treat' and the financial costs are also of course of interest.*

5 **Course after primary treatment?**
   - Should I expect a local or loco-regional recurrence?
   - Will I still have treatment options at that time?
   - Should I expect any metastases?
   - Will I then still have any curative options?
   - Should I expect complications caused by the treatment?
   *These are important questions for the follow-up. Will you be going back to see someone after the treatment? If so, what do you ask? Do you perform the standard diagnostics (blood tests, scans?) Does this patient need help or extra guidance?*
Framework oncology - points to consider (Explanatory notes)

Oncology is not a discipline of medicine with hard and fast rules. This seems like an obvious statement but is a very relevant remark at the start of this unit. One tumor will result in metastases rapidly spreading whilst another form may hardly ever metastasize or only do so at a late stage. The first metastases from the one tumor may normally be lymphogenous and the other could be hematogenous. The one kind of tumor may be best treated with surgery and the other kind would not. When metastases are found most patients are incurable, but this is not always the case (for example in a liver metastases of a colon tumor or a metastasized seminoma). For one type of tumor large-scale screening of the population makes sense, for another one it does not. Risk factors can vary enormously, the average age when the cancer starts, differences between men and women and treatment recommendations with regard to adjuvant therapy are all factors.

Not all of these differences are 'logical' and/or explainable, a (large) part of this knowledge is empirical, obtained through a long tradition of observations of patients and, of course, the natural course of their disease.

Whether a certain treatment which has proven its' usefulness for that one tumor (for example, adjuvant therapy with breast cancer), will also work with a different type of cancer (for example, colon cancer), must therefore also always be extensively researched through clinical trials. The consideration that must then be made for each tumor type is what gains have been made (the number of added years a person gains and numbers needed to treat) versus the strain on patients (side-effects, admissions, etc.) and the costs of the treatment. This balancing point will vary for the different types of tumors.

For one tumor far more diagnostic effort will be required in order to diagnose how far the disease has spread, compared with another form of cancer (staging). This depends first of all on the preliminary chance of finding something different (in other words, of the natural course and/or presentation of the disease). For a small breast tumor without affected axillary lymph nodes, the chance of there being any metastases present at diagnosis is, for example, very small. Secondly, the severity of the treatment is important. Removing the oesophagus and inserting a stoma is a major procedure with consequences for the quality of life after the surgery. Prior to such surgery you would want to have been fully informed about any metastases; if metastases are present then surgery would be pointless.

The organ/location of the tumor is a major factor when considering the available options (surgery and/or radiation) for treatment. Removing a breast is physically less invasive than removing a lung, not to mention a larynx. Radiating a brain tumor is essentially different from radiating a targeted area in the lower abdomen. Given that certain treatment options are also dictated by the anatomy, in-depth anatomical knowledge is required (for example, What is the disposition of the vascular system in the colon? What considerations must be made relating to lymph drainage of the breast?)

In oncology discussions it is regularly said "that has never shown any benefit” which means that there is no research data from which this can be demonstrated, while the concept/train of thought of proposing a certain treatment may be 'palpable' or 'logical'. A good example is using postoperative radiation therapy on an irratical resection of a carcinoma of the head of the pancreas. This is not accompanied by any conclusive data that this is useful. In addition, this is a very toxic treatment (radiation of the upper abdomen) while many patients ultimately develop metastases in the liver and die. The local recurrence as an isolated problem is far less prevalent and the importance of postoperative radiation therapy is therefore up for discussion.
4.8 Work group WG 4-1, Differences between cancers

During this work group two cases, which will be placed on Blackboard shortly prior to the beginning of the work group, will be discussed. Topics of discussion are the most common mode of presentation, clinical behavior and staging and treatment decisions that are based on this knowledge.

4.9 SSA 4-2

This SSA should be performed in preparation of lecture LT4-2: Debate on usefulness of biomarkers in cancer patients. Read the pages mentioned in the reading list to answer the questions.

Tumor markers in the diagnosis and follow-up of cancer patients.

Tumor markers are chemical substances, mostly proteins that circulate in the blood and may be elevated in patients with cancer. In clinical practice they may be helpful in establishing a diagnosis and they may also be used in the follow-up of patients with cancer after an initial treatment in order to search for an early recurrence. It is not always possible to define a clear cut-off point between normal and abnormal values. There are patients with cancer who have normal values of tumor markers. The opposite is also possible. An elevated tumor marker is not always pathognomonic for cancer.

<table>
<thead>
<tr>
<th>Tumor marker</th>
<th>Cancer type</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA</td>
<td>Most epithelial tumors, especially colorectal cancer, but may also be elevated in other cancers of the gastrointestinal tract, breast cancer, pulmonary cancer and medullary thyroid cancer</td>
<td>May be slightly elevated in smokers</td>
</tr>
<tr>
<td>CA 15.3</td>
<td>Breast cancer</td>
<td>Seldom elevated at early stage breast cancer</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate cancer</td>
<td>Cut-off point increase with age</td>
</tr>
<tr>
<td>CA-125</td>
<td>Ovarian cancer and other gynecological cancers</td>
<td>May be also elevated in patients with ascites or pleural fluid caused by benign diseases</td>
</tr>
<tr>
<td>Alfa-1-foetoproetin</td>
<td>(Extragonadal) germ cell tumors, primary liver cell cancer</td>
<td>A mass in the liver in combination with a high level of alfa-1 foetoprotein is pathognomonic for primary liver cell cancer</td>
</tr>
<tr>
<td>Beta-HCG</td>
<td>(Extra gonadal) germ cell tumors</td>
<td>Also elevated during pregnancy</td>
</tr>
<tr>
<td>CA 19.9</td>
<td>Pancreatic cancer</td>
<td>May also be elevated in benign diseases of the biliodigestive tract</td>
</tr>
<tr>
<td>S 100</td>
<td>Melanoma</td>
<td>Is seldom elevated in early stage melanoma</td>
</tr>
</tbody>
</table>
Questions:
1. What are the requirements for a good tumor marker?
2. Under which circumstances would you ask for a tumor marker in patients without a history of cancer?

Tumor markers may be used to monitor the effect of systemic treatment for those patients in whom the tumor marker is initially elevated. The primary treatment for patients with metastatic prostate cancer is directed upon the diminution of the testosterone-level in the microenvironment of prostate cancer cells. A decline in the PSA-level is an indication for successful treatment, a rise of PSA is indicative for progressive disease.

Most patients with (extragonadal) germ cell tumors have elevated levels of beta HCG and alfa-1-foetoprotein set testoro level. During chemotherapy these levels have to decline with a half time of respectively 2 and 5 days. A slower decline or increase of these values is indicative for refractory disease.

Questions:
3. How frequently do you measure tumor markers during the treatment of respectively disseminated prostate cancer and germ cell tumors?
4. Is there a different impact of the rise in the value of PSA in prostate cancer and beta-HCG and alfa-1-foetoprotein in germ cell tumors? Give an explanation

Tumor markers may be used to search for an early recurrence of cancer, in asymptomatic patients, who underwent a radical treatment for their disease.

Questions:
5. Describe in which situations you would consider to determine tumor markers mentioned above during the follow-up of one of your patients who underwent a radical treatment for cancer?
6. In which patients would you avoid determination of tumor markers?

CA-125 is a sensitive marker for the early recurrence of ovarian cancer. Determination of CA-125 several times a year was accepted as good clinical practice in the follow-up of these patients after initial treatment with debulking operation and chemotherapy. Dr. Van der Burg carried out an extensive study in this patient category to determine the usefulness of serial determination of CA-125 patients. Read this article and answer the following questions:

Questions:
7. What is a remarkable difference between the initial treatment of patients with peritonitis carcinomatosa originally from ovarian cancer and from colorectal cancer?
8. Do you advise to determine regularly CA-125 during follow-up for ovarian cancer?
9. What is your attitude if an asymptomatic patient with a medical history of ovarian cancer asks for the determination of her CA-125 level?
5. Week 5 and 6

5.1 Introduction

During this week an introduction to palliative care will be given. This is an integral aspect of oncologic care (although palliation is of course not only restricted to cancer patients) and very important. Allogeneic stem cell transplantation, cancer vaccination and immunotherapy are treatment options using the patients immune system in their approach. This is an interesting field in oncology with many opportunities in the near future. Finally the differences in endometrial and cervical cancer development will further clarify your knowledge regarding the mechanisms of cancer etiology. The use of risk adapted strategies in evidence-based treatment of cancer is another topic that will be discussed in the work group. The last lectures in this module will be dedicated to integrating all the subjects that have been taught. This will be done using clinical cases which are discussed multidisciplinary.

5.2 Week schedule

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<thead>
<tr>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
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<td>Week 5</td>
<td>LT5-1</td>
<td>Line day</td>
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| Week 6 | LT6-1   | Line day  | RL6-1    |        |
|        | LT6-2   |           | RL6-2    |        |
|        | LT6-3   |           | RL6-3    |        |
|        |         |           | Studyday | EXAM   |

5.3 Subthemes addressed during this week

From the list of themes and subthemes on page 9 the subthemes that will be addressed during these last two weeks are:

1. The etiology of malignancies
   a. Genetics and epigenetics
   b. Cancer biology
   d. Environmental factors
2. Nomenclature, staging principles and basics in treatment modalities and decisions of malignancies
   a. Nomenclature
   b. Diagnostic procedures and staging principles
   c. Basic treatment modalities and decisions
   d. Heterogeneity in cancer behavior
   e. Palliative treatment
3. Clinical and pathological aspects of the most frequent types of malignancies
   d. Prostatic cancer
4 Clinical and pathological aspects of hematological malignancies  
   b Leukemia  
   c Lymphoma  
5 Psychosocial aspects of cancer, palliative and supportive care, organization of cancer healthcare and alternative medicine (quackery)  
   c Psychosocial aspects  
   d Screening, counseling and follow-up  
   e Palliative care  

5.4 Activities  
- Study the pages indicated in the reading list below before the lectures  
- Follow the lectures (LT 5-1 – LT 5-5)  
- Perform the SSA 5-1 below  
- Prepare for and participate actively in WG 5-1  
- Attend PD 5-1  
- Follow the multidisciplinary integrating lectures LT 5-6 – LT 5-8 and LT 6-1 – LT 6-3  
- Attend RL 6-1 – RL 6-3  

5.5 Reading list  
- “Oncologie”, 8th edition:  
   Chapter 25, “Tumoren van de vrouwelijke geslachtsorganen”, pages 453-467 (upto 25.4)  
   Chapter 36, “Behandeling van pijn en andere symptomen bij de patiënt met kanker”, pages 626-642  

Additional literature:  
- Article 8: see link on Blackboard  
  Papillomaviruses and cancer: from basic studies to clinical application, Harald zur Hausen, Nature reviews 2:345-350, 2002  
- Article 9: see link on Blackboard  
  “De PORTEC trials: vooruitgang in de behandeling van endometriumcarcinoom” (NTVO 2008)  
- Article 10: see link on Blackboard  
- Article 11: see link on Blackboard  

Additional website:  
- www.oncoline.nl richtlijnen Cervixcarcinoom en Endometriumcarcinoom
5.6 Lectures, patient demonstration, case discussions and reviews

- LT 5-1: Palliative care: Introduction. This lecture will concentrate on definitions of palliative and supportive care, how to communicate, end of life decisions focusing on preserving quality of life, how to mark the start of the dying phase, aspects of euthanasia.
- LT 5-2: Palliative care: Causal treatment options. In this lecture the effectiveness of radiotherapy, surgery, systemic therapies as treatment modalities in the palliative phase are discussed, including the question how long and how far should patients actively be treated.
- LT 5-3: Palliative care: Pain and other symptoms. This lecture will focus on the mechanisms, active treatment options, and supportive care, including terminal care such as palliative sedation.
- LT 5-4: Allogeneic stem cell transplantation. In this lecture the principles of allogeneic stem cell transplantation will be discussed with emphasis on T cell depletion of the stem cell graft and treatment of patients with cellular immunotherapy (donor lymphocyte infusion, DLI) to enhance the allo-immune effect in order to cure the disease.
- LT 5-5: Cancer and immunity, vaccinations. In this lecture the possible role of the immune system in the treatment of cancer will be discussed, including the escape mechanisms of cancer cells to normal immune processes, immunotherapy and vaccination.

- PD 5-1: Patient demonstration, Allogeneic stem cell transplantation: During this patient demonstration the physical and emotional impact of allogeneic stem cell transplantation followed by DLI on everyday life will be discussed with a patient.

- LT 5-6: Case discussion Hereditary melanoma: In this lecture a patient with hereditary melanoma is presented. Using this case the genetic aspects of melanoma, implications of a genetic trait for the patient and his family, staging of melanoma, local and systemic treatment options and organization of treatment of patients with disseminated melanoma in the Netherlands will all be alluded to.
- LT 5-7: Case discussion Lymphoma: In this lecture diagnosis and treatment of a patient with lymphoma will be discussed in a multidisciplinary session.
- LT 5-8: Case discussion Metastatic prostate cancer
- LT 6-1: Case discussion Paraneoplastic thrombotic events
- LT 6-2: Case discussion Palliative and supportive care
- LT 6-3: Case discussion Chemoradiation

- RL 6-1: In this summarizing lecture the highlights of the different topics of hematological disorders (bleeding, thrombosis and atherosclerosis), discussed during the course, will be shown, including some MC-questions in preparation for the final exam. Of course students will have the ability to answer questions (Vlijmen).
- RL 6-2: In this summarizing lecture the highlights of the different topics of hematological malignancies, discussed during the course, will be shown, including some MC-questions in preparation for the final exam. Of course students will have the ability to answer questions (Marijt).
- RL 6-3: In this summarizing lecture the highlights of the different topics of solid tumors, discussed during the course, will be shown, including some MC-questions in preparation for the final exam. Of course students will have the ability to answer questions (Neelis/Smit).
5.7 SSA 5-1

Introduction

Cervical cancer and endometrial cancer are the most frequent gynecological cancers worldwide: while cervical cancer is most common cancer in women in developing countries, endometrial cancer is the most common gynecological cancer and the fifth most common cancer in women in developed countries. In those countries, endometrial cancer incidence is rising related to increased life expectancy and increased obesity, while the incidence of cervical cancer has decreased due to effective screening programs and is expected to further decrease as a result of vaccination programs. In developing countries, however, cervical cancer continues to be a significant women’s health problem and programs for screening and early diagnosis are only available in some regions.

The mechanisms of cancer development in cervical and endometrial cancer are completely different. Cervical cancer development starts with persistent high-risk HPV viral infection at the transformation zone of the cervix, and after introduction of viral RNA in the host cells invasive cancer gradually develops via dysplastic and pre-malignant changes in the epithelium. Endometrial cancer most often develops from dysregulated proliferative changes in the endometrium induced by continued hormonal stimulation and frequently accompanied through multiple genetic alterations, such as PTEN loss and PIK3CA and KRAS mutations.

Treatment principles of cervix and endometrial cancer have been based on surgical approaches (hysterectomy or radical hysterectomy) and radiation therapy, either as primary or as adjuvant treatment. Since 2000 chemotherapy has been introduced in the standard treatment approaches. Principles of primary and adjuvant treatment and the role of prognostic clinico-pathological and molecular factors to tailor the indication of adjuvant treatment will be studied to understand the development of evidence-based treatment approaches. The challenge is to avoid overtreatment of women with low risk of recurrence, but improve survival and recurrence-free survival for those at higher risk. Molecular factors may improve the current clinic-pathological risk assessment and help to understand the mechanisms of dedifferentiation of cancer and of early invasion and metastatic potential.

Please use the literature to answer the following questions in preparation for work group WG 5-1 Gynecologic tumors.

1. What are the incidence and mortality rates of cervical and endometrial cancer in the Netherlands?
2. What is the main etiological factor involved in cervical cancer? By which mechanism contributes this factor to cervical cancer development? Which oncogenes or tumor suppressor genes are involved?
3. What are the morphological differences between a cervical squamous cell carcinoma and cervical adenocarcinoma, and which criteria are used by the pathologist to discriminate these two entities?
4. What are the main etiological factors involved in endometrial cancer? To what extent do hormonal factors play a role in the etiology of cervical or endometrial cancers? What types of hormonal factors? Why do we have a screening program for cervical cancer, but not for endometrial cancer? Explain how this screening program has been organized in the Netherlands and how the HPV vaccination program will affect this system in the coming years.
5. Describe the premalignant phases and precursor lesions of cervical cancer and endometrial cancer respectively.
6. Which staging system is used for gynecological cancers? Please describe this staging system for cervical and endometrial cancer and how this relates to the TNM classification.
Which different types of cervical and endometrial cancer are used in the WHO-classification and which types are most frequent?

Which treatment options are currently used for cervical and endometrial cancer? Describe the principles of adjuvant therapy. To what extent is the indication for adjuvant treatment dependent on stage and/or risk factors?

Describe the impact of the PORTEC trials on treatment guidelines and on patient counseling.

What is the driving molecular alteration in serous endometrial cancer?

Explain what is meant with microsatellite instability (MSI) and describe the underlying mechanism of MSI development in both “sporadic” and hereditary endometrial cancer.

Which information do you as a clinician need from the pathologist to decide whether a patient with endometrial cancer needs any adjuvant treatment?

5.8 SSA 5.2

In addition please study the following cases and prepare a short (10 min) Powerpoint presentation (max 8 slides) for work group WG 5-1 Gynecologic tumors.

Students 1-3 of the work group; please prepare questions 1-4 (4 slides) of case 1
Students 4-7 of the work group; please prepare questions 5-8 (4 slides) of case 1
Students 8-10 of the work group; please prepare questions 1-4 (4 slides) of case 2
Students 11-15 of the work group; please prepare questions 5-8 (4 slides) of case 2

Case 1 [see pedigree below]
Marloes, 29 yrs of age, had symptoms of irregular blood loss and post-coital bleeding, 2 months after stopping OAC in view of active wish for pregnancy. A cervical smear was done by the GP: Pap 3B.
Clinical examination and a loop excision of the cervix showed adenocarcinoma, FIGO stage IB1 (slide 1). She was counseled on the situation and treatment options, and subsequently underwent laparotomy with the aim to perform fertility-conserving surgery, i.e. radical trachelectomy after pelvic lymph node dissection. However, during surgery a firm, enlarged (1.5 cm), suspicious lymph node was found in the right deep internal iliac region, and was sent for frozen section. The pathology result was metastatic adenocarcinoma. In view of this result the operation was modified, and after lymph node dissection the left ovary was suspended upwards, and fixed to the anterior abdominal wall on the left side above the umbilical level. The uterus and cervix remained in situ. Final pathology (slide 2) showed lymph node metastases in 2 of the 33 removed lymph nodes, respectively in the right and left deep internal iliac regions.

In slide 3 the same lymph node is shown on which a p16 immunohistochemical staining has been performed.

Questions:
1 Describe the main etiologic factor and the risk factors for this type of cancer. Describe the premalignant phase and precursor lesion. Does adenocarcinoma of the cervix differ from squamous cell carcinoma, and if yes, in what ways?
2 Explain the mechanism by which p16 overexpression can be found in this lesion.
3 Describe the FIGO clinical staging system and consequences for standard treatment by stage. Was the FIGO stage altered after surgery? Describe the cTNM and pTNM stage for this patient.
4 Describe the differences between a trachelectomy and a radical hysterectomy.
5 What are the treatment consequences of the lymph node metastases? Why was the type of surgery modified? Why was the uterus left in situ?
A MRI scan of the pelvic region showed post surgical changes, no clear residual tumor after the loop excision, no remaining enlarged lymph nodes (slide 4). She underwent chemoradiation and brachytherapy (slide 5).

Questions:
6 Why was the MRI scan done? Describe the role of imaging for staging and treatment of cervical cancer.
7 Describe the preferred treatment for cervical cancer with lymph node metastases. Describe the dosage and type of treatment(s), main techniques, and main side effects and probability of local control and survival rates.
8 Describe the post treatment rehabilitation and counseling principles. What follow-up investigations should be done and why? What difficulties will this patient encounter after the treatment phase?

Case 2 [see pedigree below]
Her mother-in-law, Indira, 60 years of age, had symptoms of vaginal bleeding as well. She has a history of hypertension, her BMI is 33, she has had three pregnancies (Chantal, Dennis and Mitchell). She had been taking hormonal replacement therapy (HRT, tibolon 2.5 mg once daily) for menopausal symptoms since 20 years. Her annual pap smear had always been OK (PAP 1-2), and bi-annual mammogram had always been OK. She had a vaginal ultrasound, which showed an intracavitary polyp (slide 1). She underwent hysteroscopy with resection of the endometrial polyp. The polyp consisted of endometrial tissue with extensive hormonal changes (slide 2) and multiple foci of endometrioid adenocarcinoma, grade 1 of the endometrium (slide 3). Additional immunohistochemistry (IHC) and molecular genetic analysis showed loss of expression of MLH-1 and PMS2 (slide 4), loss of PTEN expression, the presence of a KRAS mutation and an exon 3 beta-catenin mutation (slide 5). P53 IHC shows a normal wild type.

Questions:
1 What are the risks and benefits of taking HRT (opposed or unopposed) estrogens in the postmenopausal phase? She underwent annual pap smears – was this type of screening aimed at the risks of HRT? Did you find etiologic factors in her history?
2 Explain the immunohistochemical results especially the loss of MLH1 and PMS2 expression. What mechanism is probably the underlying cause of this phenomenon? What subsequent investigations should be done?
What is the implication of a beta-catenin mutation? Which pathway is probably activated due to this genetic alteration and what immunohistochemical result of a beta-catenin staining can be expected in the tumor cells?

What is the clinical stage and the standard treatment for this case?

Mrs Indira Dekker underwent laparoscopic hysterectomy and bilateral salpingo-oophorectomy. She had a rapid recovery. Final pathology showed a grade 1 endometrioid endometrial carcinoma with myometrial invasion to just over 50% of the myometrial width. Tumor free distance to the serosa 5 mm. No lymph-vascular invasion, no endocervical extension, ovaries not involved.

Questions:

What is the post-surgical FIGO and TNM stage? Would she have an indication for adjuvant treatment according to the current Dutch national guidelines? Which type?

Is your proposal for offering adjuvant treatment influenced by the molecular results and if so explain the rationale of this?

What would be the pros and cons of adjuvant treatment, both on a personal level and health care level (cost benefit ratio)? What would you recommend? Would she be eligible for one of the randomised PORTEC trials? If so, in which of those trials would she be a candidate? Please discuss the background and objectives of the trial.

What type and frequency of follow-up would be appropriate? What would be the main purpose of follow-up?

5.9 Work group WG 5-1, Gynecological tumors

During this work group the two cases, which you have prepared in advance (see SSA 5-2) by making a power point presentation, will be discussed with focus on clinical presentation, etiological and pathological aspects, genetic and immunological factors, diagnostic procedures, risk assessment, different treatment modalities, principles of follow-up. During the work group each of the students will be asked to present part of their power point.
The students have prepared the cases according to this schedule:
Students 1-3 of each work group have prepared questions 1-4 (4 slides) of case 1
Students 4-7 of each work group have prepared questions 5-8 (4 slides) of case 1
Students 8-10 of each work group have prepared questions 1-4 (4 slides) of case 2
Students 11-15 of each work group have prepared questions 5-8 (4 slides) of case 2

So in each work group half of the students (no 1-7) have prepared case 1 (cervical cancer) and the other half of the students (no 8-15) have prepared case 2 (endometrial cancer) by answering the questions belonging to the cases (see SSA 5-2 above).
6. Attachment A: Leukemia and lymphomas

6.1 Hematopoiesis

6.1.1 Development of the blood-forming organs and blood cells

In the 3rd week of pregnancy the formation of the first hematopoietic cells occurs in the vessels of the extra-embryonic mesenchyma of the yolk sac, the chorion and umbilical cord. These vessels contain a large amount of hematopoietic precursor cells, which migrate through the embryonic vessels to the liver. Hematopoiesis, which takes place extravascularly in the liver, begins in the 5th and 6th week of pregnancy. It is assumed that at the end of the second month the spread of cells begins from the liver to the lymphoid organs (thymus, spleen) and then later to the lymph nodes. Hematopoiesis begins more or less simultaneously in several bone marrow cavities. Through the penetration of mesenchymal cells into the bone cavities, a stroma of loosely meshed connective tissue is created. After a few weeks, the stroma is able to absorb the incoming hematopoietic cells and allow them to develop. The actual production of blood cells in the bone marrow only commences after the fifth month.

In normal adults, the bone marrow is located in the marrow cavities of the vertebrae, ribs, sternum, pelvis, shoulder blades, skull, and the most proximal portions of the femora and humeri. The marrow cavities of the remaining bone are filled with fatty tissue. In children, the bone marrow is also located in the more distal parts of the extremities.

The marrow cavities in the bone are partially compartmentalized by trabeculae that protrude in the cavities creating a labyrinth of communicating spaces. The entire inner surface of the bone is covered with the endosteum consisting of osteoblasts and osteoclasts. Oxygenated blood reaches the blood-forming cells of the bone marrow through supply arteries that penetrate the bone, branch off into smaller arteries and capillaries and connect to the extensive venous sinus system, which in its turn is in contact with the draining veins.

Blood-forming bone marrow cells are located in gelatinous material embedded in reticular stroma tissue between the trabeculae and the venous sinuses. The location of the various hematopoietic cells in the bone marrow is of great significance to their release into the bloodstream. The megakaryocytes and erythropoietic islands are close to the venous sinuses. Myelopoiesis takes place along the trabeculae; mature segmented granulocytes are also located rather closely around the venous sinuses. Because of this special location, the release of mature blood cells to the blood stream is facilitated.

6.1.2 Normal hematopoiesis

The basic premise for all of hematopoiesis is that all cell lines develop from a pluripotent stem cell. This is a cell which is capable, through division, of both maintaining itself (self-renewal) and maturing into cells of all differentiation lines (lymphatic and myeloid). Morphologically this stem cell has no specific characteristics in humans, and it is most similar to a small lymphocyte. The stem cell must be activated for DNA synthesis, division and further differentiation.

The existence of a common stem cell (pluripotent stem cell) for both cell lines that develops into erythrocytes, granulocytic cells and thrombocytes and for lymphocytes, respectively, has thus far not been demonstrated, but on the basis of transplantation experiments this is indeed quite probable. In bone marrow cultures in vitro, under certain circumstances colonies of cells may be created from the various differentiation lines. These colonies are assumed to originate from a stem cell committed for that cell line. They are referred to as ‘colony forming units’ (CFU) and are named after the cell series resulting from this. The CFU-GM, for example, specifies the stem cell for the granulocytic-monocytic series and BFU-E and CFU-E for erythrocytes. For the cultivation of a certain type of precursor cell, however, a number of
specific conditions including the presence of hematopoietic growth factors are necessary. For example, the earliest erythroid stem cell (BFU-E) does not depend on erythropoietin for its growth, but further differentiated cells along the erythrocytic line do. Necessary for the growth of BFU-E are growth factors produced by monocytes and/or T-lymphocytes. Growth factors (‘colony stimulating factors’) are necessary as well for the granulocytic-monocytic series (CFU-GM) and are produced by leukocytes (monocytes and lymphocytes), endothelial cells, fibroblasts and other accessory cells. Thrombopoietin has an influence on the growth and differentiation of megakaryocytic precursor cells into thrombocytes. Lymphocytic stem cells are also generated in the bone marrow compartment and are also derived from the pluripotent hematopoietic stem cell. Not only in the earliest phase of B- and T-cell development but also in the later phases such as during the follicular centre reaction, cells are able to self-renew and form differentiating daughter cells.

Upon an increase in the demand for differentiated cells, the committed cell compartment divides and differentiates, resulting in a temporarily increased production of mature cells. If this compartment is damaged or insufficient, the pluripotent stem cells are activated, allowing renewal of the committed stem cell compartments. Varying amounts of the bone marrow cavities are occupied by fat cells.

Examination of the bone marrow is done, under local anaesthesia, with the aid of bone marrow aspiration or bone marrow biopsy. This must always be accompanied by morphological examination of peripheral blood (blood smear). A normal bone marrow aspirate consists of 50-60% precursors and mature cells of the neutrophilic series, 3% of cells of the eosinophilic series, <0.1% of the basophilic series, 20-25% of the erythroid series, 15-20% of lymphocytes and plasma cells, and <0.1% megakaryocytes.

6.2 Origin, kinetics and regulation of leukocytes

6.2.1 Introduction

Leukocytes can be subdivided as neutrophilic, eosinophilic and basophilic granulocytes, monocytes and lymphocytes. All higher animals have two types of phagocytic cells: polymorphonuclear leukocytes (granulocytes) and mononuclear phagocytes.

Phagocytizing cells not only have a central place in the defence against infections and malignancies but can also endocytose antibody complexes, necrotic tissue and senescent cells. Both of these cell types are produced in the bone marrow. The mature cells are transported by the blood and eventually end up in the tissues where they exert their functions. There, on the one hand, monocytes can mature into macrophages, as well as into histiocytes that for the most part lose their phagocytizing function, but are more specialised in cytokine production: the epithelioid cell that among other things plays a central role during granuloma formation. In addition, there is a separate type of cell (dendritic cell) that develops from the monocyte and that is specialised mainly in antigen presentation: from these cells the Langerhans cells develop in the skin and the interdigitating cells in the lymph nodes.

6.2.2 Origin and kinetics of granulocytes

Granulocytes are formed in the bone marrow by cell division and differentiation. Differentiation also occurs after the moment when the capacity to divide is lost. Segmented granulocytes spend a few days in the bone marrow before they are released into the blood, where they circulate for a short time (hours) and then disappear into the tissue. Analysis of the cycle of human bone marrow cells indicates that the earliest recognizable myeloid cells (myeloblasts and promyelocytes) each undergo one division. Myelocytes can divide two more times. The differentiation from myelocytes to segmented granulocytes requires at least 48 hours. Cells are constantly entering the postmitotic compartment (metamyelocytes, rod-shaped and
segmented granulocytes). This compartment serves as a storage pool: segmented granulocytes remain here for 3-5 days. Release from the bone marrow into the blood occurs on the basis of the age of the cell. Cell kinetic studies indicate that the number of granulocytes in the capillary vascular bed is approximately 2x as large as in the circulation. In small blood vessels, there is a rapid, central flow and a slowly moving layer of cells up against the vessel wall. In this slow flow, cells can temporarily adhere to the endothelial surface. These ‘marginal’ granulocytes can quickly exchange with the ‘circulating’ cells, for example during exercise or the administration of adrenalin. The number of circulating neutrophilic granulocytes in the blood of adults is approximately 3-4x10^9/L, while an equally large number of them are in the marginal pole. Half of these granulocytes are replaced every 6 hours. The granulocytes leave the circulation at a time that is independent of their age. The fate of this large number of granulocytes is not known with certainty. It is probable that most granulocytes exercise their function in and on the mucosa of the respiratory tract, urogenital and gastro-intestinal tracts and that they leave the body via these mucous membranes. The lifetime of neutrophilic granulocytes is about 5.5 days. Part of the aged granulocytes returns to the bone marrow cavity and plays a role in the regulation of the production of new hematopoietic precursor cells.

The immediate response of the granulocytic system to a bacterial or sterile inflammation is neutropenia due to increased margination of granulocytes and accelerated delivery of neutrophilic granulocytes into the affected tissues. Within an hour, large numbers of neutrophils move from the postmitotic compartment in the bone marrow into the blood. This leads to neutrophilic leukocytosis and a clear left shift (the increase in the ratio of the rod-shaped/segmented granulocytes); Doehle-bodies (aggregates of endoplasmic reticulum), and toxic granulation (large, azurophilic granules) of the neutrophilic granulocyte cytoplasm are characteristic.

6.2.3 Mononuclear phagocytes
The term ‘mononuclear phagocytes’ is the group name for monocytes, macrophages and their precursors. Monocytes leave the bone marrow within 24 hours after their production, circulate for some time in the blood and then migrate to the tissue where they become macrophages or other more specialised cells (see above).

6.2.4 Lymphocytes
The development of T- and B-lymphocytes comprises various phases that occur in specific compartments (bone marrow, blood, peripheral lymphoid tissues for B-cells; bone marrow, blood, thymus and peripheral lymphoid tissues for T-cells). Both lines have an early phase of active division of precursor cells, a phase of circulating in the blood, and a last stage of activation and proliferation of mature forms in peripheral lymphoid tissues. This last phase, in particular, is influenced by such factors as antigenic stimulation. T-cells already develop to T-helpers or T-suppressor cells in the thymus. B-cells eventually develop into plasma cells. This development can take place directly (plasma cell reaction) but also after a phase of active division in the follicle centre cell reaction. An important part of plasma cells, and thus immunoglobulin production, is located in an adult human in the bone marrow (after migration from peripheral lymphoid tissues?). For more detailed information about the lymphoid system, the reader is referred to the module Mechanisms of Disease 1.

6.2.5 Leukocytopenia and leucocytosis
The normal number of leucocytes in the blood of adults and children over 14 years ranges from 4-10 x 10^9/L. If the total is more than 10 x 10^9/L leucocytosis is present; if it is less than 4 x 10^9/L there is leucocytopenia. The normal values are shown in Table 1.
One speaks of neutrophilic granulocytosis or neutrophilia if the neutrophil count is greater than 7 x 10^9/L. Depending on the cause (infections, inflammation, tissue death, malignancies, hematopoietic conditions etc.) sometimes values of more than 50-100 x 10^9/L can be found.

In neutrophilic granulocytopenia or neutropenia, one finds a decrease in the absolute number of neutrophils to under 1.5 x 10^9/L (Classification: see Table 2). This decrease leads to reduced resistance to bacterial and fungal infections, but a clearly increased risk of infection only exists at much lower values (under 0.5 x 10^9/L). In addition, the monocytes also play a role, which, if present, can still provide some protection. If there is also monocytopenia, many serious infectious complications occur. The term agranulocytosis is used in very severe neutropenia (<0.5 x 10^9/L).

Table 1. Normal blood leukocyte values in adults (Wintrobe, Textbook of Clinical Hematology)

<table>
<thead>
<tr>
<th></th>
<th>Median x 10^9/L</th>
<th>Range x 10^9/L</th>
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<tbody>
<tr>
<td>Leukocytes</td>
<td>7.0</td>
<td>4 - 10</td>
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<tr>
<td>Rod-shaped neutrophils</td>
<td>0.52</td>
<td>0.1 - 2.0</td>
</tr>
<tr>
<td>Segmented neutrophils</td>
<td>3.0</td>
<td>1.5 - 6</td>
</tr>
<tr>
<td>Neutrophils total</td>
<td>3.65</td>
<td>1.5 - 7</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.15</td>
<td>0.1 - 0.7</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.03</td>
<td>0 - 0.15</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.43</td>
<td>0.2 - 0.9</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>2.5</td>
<td>1.5 - 4.0</td>
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</table>
Table 2. Pathogenetic classification of neutropenia

<table>
<thead>
<tr>
<th></th>
<th>Reduced granulopoiesis</th>
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<tbody>
<tr>
<td></td>
<td>Bone marrow hypoplasia, primary or secondary, due to medications, toxins, radiation,</td>
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<tr>
<td></td>
<td>malignant diseases, auto-immune diseases, aplastic anemia</td>
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<td></td>
<td>Rare production disorders: cyclic or chronic neutropenia.</td>
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<tr>
<td></td>
<td>Ineffective granulopoiesis</td>
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<tr>
<td></td>
<td>With normocellular or hypercellular dysplastic bone marrow, in conjunction with</td>
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<tr>
<td></td>
<td>megaloblastic anemia, myelodysplasia, drugs that interfere with folate metabolism</td>
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<tr>
<td></td>
<td>(methotrexate, diphenylhydantoin, trimethoprim)</td>
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<tr>
<td></td>
<td>Increased granulopoiesis</td>
</tr>
<tr>
<td></td>
<td>A number of serious bacterial or viral infections, sepsis, diseases with splenomegaly</td>
</tr>
<tr>
<td></td>
<td>(hypersplenism)</td>
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<tr>
<td></td>
<td>Diseases with circulating immune complexes, in vivo complement activation, autoantibodies against</td>
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<tr>
<td></td>
<td>neutrophils</td>
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<tr>
<td></td>
<td>Drug-induced immune responses resulting in neutropenia</td>
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<tr>
<td></td>
<td>Combinations</td>
</tr>
<tr>
<td></td>
<td>In sepsis, by autoantibodies, through drug-induced immune responses</td>
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</tbody>
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6.3 Hemato-oncology

6.3.1 Introduction

*Malignant disorders in hematology involve neoplasms of hematopoiesis in the bone marrow (hence the name myeloproliferative disorders) or of lymphopoiesis (lymphoproliferative disorders).*

The main disorders are shown in Table 3. These diseases are characterized by a clonal and often uncontrolled proliferation of mature or immature cells. Only the diseases printed in bold in Table 3 will be dealt with in this module Mechanisms of disease 2.

If the proliferation occurs primarily in the bone marrow and malignant cells secondarily move around via the bloodstream, leukemia is present. If the proliferation occurs primarily in lymphoid tissues (thymus, lymph glands, spleen, other lymphoid tissues) and involves B- or T-lymphocytes, it is called a malignant lymphoma. This terminology is thus based on the clinical presentation. To make things more complicated, lymphomas can also present with malignant cells in the peripheral blood: leukemic lymphomas. For the WHO classification that is based mainly on cell-biological characteristics, this difference is subordinate.
### Table 3. Classification myeloid and lymphocytic disorders

**MYELOID**

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Acute myeloid leukemia and related precursor neoplasms</td>
</tr>
<tr>
<td></td>
<td>- <strong>Acute myeloid leukemia (AML)</strong></td>
</tr>
<tr>
<td>II</td>
<td>Myelodysplastic syndromes</td>
</tr>
<tr>
<td>III</td>
<td>Myeloproliferative neoplasms:</td>
</tr>
<tr>
<td></td>
<td>- <strong>Chronic myeloid leukemia (CML)</strong> <em>(proliferation of granulocytic cells)</em></td>
</tr>
<tr>
<td></td>
<td>- Polycythemia vera <em>(proliferation of mainly erythropoiesis)</em></td>
</tr>
<tr>
<td></td>
<td>- Idiopathic myelofibrosis <em>(proliferation of megakaryopoiesis without complete maturation)</em></td>
</tr>
<tr>
<td></td>
<td>- Essential thrombocytosis <em>(proliferation of megakaryopoiesis with maturation)</em></td>
</tr>
<tr>
<td>IV</td>
<td>Aplastic anemia <em>(an immune-mediated disease)</em></td>
</tr>
</tbody>
</table>

**LYMPHATIC**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>V</td>
<td>Neoplasms of lymphoid precursors</td>
</tr>
<tr>
<td></td>
<td>- <strong>Acute lymphocytic leukemia (ALL)</strong></td>
</tr>
<tr>
<td>VI</td>
<td>Neoplasms of mature B- or T-lymphocytes <em>(chronic lymphocytic leukemia (CLL), Non-Hodgkin’s lymphoma (NHL))</em></td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>VII</td>
<td>Hodgkin’s lymphoma:</td>
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<tr>
<td></td>
<td>- Nodular lymphocyte predominant Hodgkin’s lymphoma</td>
</tr>
<tr>
<td></td>
<td>- <strong>Classical Hodgkin’s lymphoma (HL)</strong></td>
</tr>
</tbody>
</table>

### 6.4 Malignant myeloid diseases

#### 6.4.1 Introduction

In these diseases of the bone marrow, there is clonal and autonomic proliferation of a (committed) precursor cell that results in expansion of one or more cell lines of the hematopoietic system. If this proliferation is accompanied by a differentiation stop (so that only expansion takes place; no differentiation and no apoptosis), acute myeloid leukemia *(AML)* occurs whereby the tumor cells can be morphologically recognised as blasts. Myeloid malignancies, in which the proliferation rate is unrestrained but normal maturation still takes place, are termed myeloproliferative disorders. While the various subtypes of AML are clinically rather strongly alike, myeloproliferative disorders differ significantly in their clinical picture, depending on the cell line(s) that are affected (increase in granulocytes, erythrocytes, and/or thrombocytes).

#### 6.4.2 Acute myeloid leukemia (AML)

Acute myeloid leukemia is a clonal disease of the bone marrow in which malignant precursor cells proliferate and show a maturation defect. This leads to rapid expansion and accumulation of immature cells (blasts) in the bone marrow, whereby these cells also begin circulating in the blood. In a few weeks or months, the number of leukemia cells can increase to $10^{12}$ or more, which comes down to a tumor of a
kilogram or several kilograms. These cells accumulate, first in the bone marrow and later in the blood, and suppress the normal blood cell production. This means that the blood film of a patient with AML will often show severe anemia and thrombocytopenia. Usually the number of leukocytes has increased significantly (primarily blasts) but sometimes there may be leukopenia. Acute leukemia, therefore, commonly presents with symptoms due to anemia, bleeding and/or infection. Liver and spleen enlargement are usually not prominent. Sometimes, through obstruction of blood vessels by leukemic blasts in the lungs and brain, there is shortness of breath and drowsiness ('leucostasis'). Bone pain can occur due to bone necrosis or rapid expansion of leukemia cells in the bone marrow. Serious, life-threatening bleeding due to disseminated intravascular coagulation occurs frequently in acute promyelocytic leukemia (APL). This coagulopathy is caused by a number of factors that have to do with the APL: APL cells produce two pro-coagulant factors: Tissue factor (TF) and cancer procoagulant (CP): there is increased fibrinolysis: production of tissue-type plasminogen activator (t-PA), reduction of plasminogen and alpha2-antiplasmin concentration, increased expression of Annexin-II on endothelial cells of the cerebral vessels (this may explain the increased tendency toward cerebral hemorrhage in APL patients) and increased cytokine production: IL-1 beta and TNF-alpha: they change a normal anti-coagulant endothelial surface into a pro-coagulant surface.

Incidence
The incidence of AML is approximately 3/100,000 inhabitants per year. The frequency increases with age. About half of all patients are older than 60 years.

Etiology and pathogenesis
Although the etiology of AML is unknown, some factors are known that can predispose for the occurrence of this disease. Increased frequency is noted in persons that have been exposed to ionizing radiation (survivors of the atomic explosions in Japan), approximately 5-7 years after the exposure. Long-term exposure to the toxic effects of certain chemical substances also increases the risk of this condition. One sees this in people who professionally come in contact with benzene, organic solvents, dyes, etc. In recent years it has become clear that AML can also occur (several years) after intensive chemotherapy for other cancers: for example 1-2% of patients with Hodgkin's lymphoma who have undergone intensive treatment with alkylating agents develop (secondary) acute myeloid leukemia (see above) 2-6 years later. Genetic factors play a yet unclear role in the development of AML, as evidenced for example by the increased incidence of acute leukemia in patients with some congenital diseases (e.g. Down's syndrome). A viral genesis of AML, such as often occurs in animals, has hitherto not been demonstrated in humans. In more than half of patients with AML, characteristic cytogenic changes occur in the tumor cells. Molecular studies have contributed to our understanding of the pathogenesis of AML and may provide opportunities for targeted therapy. This is illustrated by the reciprocal translocation between chromosomes 15 and 17 (t(15;17)) in acute promyelocytic leukemia. In this translocation the gene coding for the retinoic acid receptor is involved; disruption of this gene leads to maturation inhibition of the tumor cells. Administration of high doses of vitamin A derivative (all trans retinoic acid = ATRA) stimulates the maturation of tumor cells into normal neutrophilic granulocytes. Therapy with ATRA has therefore considerably improved the prognosis.

Laboratory findings
Analysis of peripheral blood often shows anemia and thrombocytopenia. The number of white cells can range from marked leucocytopenia to extreme leucocytosis, which then consists almost solely of immature (blast) cells. Usually the bone marrow is rich in cells and contains a great deal (20-100%) of immature and monotonous blast cells with myeloid characteristics. These myeloid characteristics consist of peroxidase
or Sudan Black positivity (cytochemical or immunologically detectable) or the presence of myeloid markers (and absence of lymphatic markers!) upon immunophenotyping.

In addition, a large number of cytogenetic (= chromosome) aberrations can be found in the leukemic cells. These aberrations have prognostic value. Patients with the following aberrations have the best prognosis: t(8;21), inversion16, t(15;17), and isolated mutation of the NPM1 gene. Patients with a (partial) deletion of chromosomes 5 or 7, t(6;9), a complex karyotype abnormality (>3 clonal deviations per cell), or a monosomal karyotype (≥ 2 autosomal monosomies or 1 autosomal monosomy plus ≥ 1 structural chromosomal aberrations) have the worst prognosis. The remaining patients with other cytogenetic abnormalities plus patients with a ‘normal’ chromosome pattern in the leukemia cells have an intermediate prognosis.

In 2001 and again in 2008, the WHO (World Health Organisation) has composed a classification for acute myeloid leukemia that is based mainly on cytogenic and molecular abnormalities. A separate category was created for AML cases that demonstrate a strong resemblance to myelodysplastic syndrome or that are the result of prior chemotherapy. The leukemias that do not fall into these groups and differ mainly in morphological characteristics are classified in a residual group that has many similarities to the old FAB classification (see the figure ‘Appendix: WHO classification Acute Myeloid Leukemia’). It is expected that in the coming years more molecular abnormalities will be found and that over the course of time these will also be included in the new WHO classification.

### WHO classification Acute Myeloid Leukemia and related precursor neoplasms

<table>
<thead>
<tr>
<th>Acute Myeloid Leukemia Blasten &gt; 20% (in blood and/or bone marrow)</th>
<th>I. AML with recurrent cytogenetic abnormalities:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent cytogenetic aberrations?</td>
<td>AML t(8;21)(q22;q22)</td>
</tr>
<tr>
<td>yes</td>
<td>Acute promyelocytic leukemia with t(15;17)(q22;q11-12)</td>
</tr>
<tr>
<td>no</td>
<td>AML (inv16)(p13;q22) of t(16;16)(p13;q22)</td>
</tr>
<tr>
<td>yes</td>
<td>AML with 11q23 (MLL) abnormality</td>
</tr>
<tr>
<td>NPM1 mutation</td>
<td>CEBPo mutation</td>
</tr>
<tr>
<td>Inv(3;3)</td>
<td>t(1;22)</td>
</tr>
<tr>
<td>t(6;9)</td>
<td>t(9;11)</td>
</tr>
<tr>
<td>Therapy related?</td>
<td>no</td>
</tr>
<tr>
<td>yes</td>
<td>III. AML (and MDS) therapy related</td>
</tr>
<tr>
<td>AML as a side effect of alkylating agents: [3q1, 5, 7, 8, 9, 11q, 12p, 14p, 18, 20p, +21] t(1;7), (t;2;11)</td>
<td></td>
</tr>
<tr>
<td>AML after topoisomerase II inhibitors: 11q23, t(8;21), t(15;17), Inv16</td>
<td></td>
</tr>
<tr>
<td>Other AML due to prior chemotherapy</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>IV. AML not otherwise specified:</td>
</tr>
<tr>
<td>AML with minimal differentiation</td>
<td></td>
</tr>
<tr>
<td>AML without maturation</td>
<td></td>
</tr>
<tr>
<td>AML with maturation</td>
<td></td>
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<tr>
<td>Acute myelomonocytic leukemia</td>
<td></td>
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<tr>
<td>Acute monoblastic/monocytic leukemia</td>
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<tr>
<td>Acute erythroid leukemia</td>
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<tr>
<td>Acute megakaryocytic leukemia</td>
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<tr>
<td>Acute basophilic leukemia</td>
<td></td>
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<tr>
<td>Acute panmyelosis with myelofibrosis</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>V. Myeloid sarcoma</td>
</tr>
<tr>
<td>no</td>
<td>VI. Myeloid proliferaions rel. Down syndrome</td>
</tr>
<tr>
<td>yes</td>
<td>VII. Blastic plasmacytoid dendritic cell neoplasm</td>
</tr>
</tbody>
</table>
Natural course
The natural course of AML is infaust, with patients only surviving for a few weeks to months.

Treatment
Remission induction and consolidation. The strategy of remission induction treatment makes use of the fact that leukemic cells are more vulnerable than healthy precursor cells for cytotoxic effects of a number of chemotherapeutic agents (cytosine arabinoside, anthracyclines). After the leukemic cell mass is reduced, the remaining normal stem cells can proliferate and mature into normal blood cells. One of the pillars of remission induction therapy is to quickly achieve a profound reduction of leukemic cells:
- Quickly, in order to keep the life-threatening period of lack of normal bone marrow (risk of infections and bleeding) as short as possible and expose the remaining healthy stem cells to chemotherapy for the shortest possible amount of time.
- As completely as possible, because the chance of complete remission and a long recurrence-free period is dependent on the extent to which the leukemic population can be eradicated.

If the bone marrow morphologically contains less than 5% blasts, is normocellular and the peripheral blood values have normalised the patient has reached a complete remission. With treatment protocols containing an anthracycline and cytosine arabinoside, in 70-80% of patients under 60 years and in about 50% of patients over 60 years a complete remission is achieved after one or two courses of treatment. During the phase of ‘active’ leukemia, the total number of blasts in the body is about $10^{12}$ cells (= about 1 kg). If > 99% of this is eradicated, the leukemia can no longer be morphologically demonstrated, although the body can still accommodate $10^8$-$10^{10}$ leukemia cells! In the hope of thus achieving further cell reduction to, for example, $10^8$ or $10^6$ or fewer remaining leukemic cells, another one or two courses of treatment, so-called consolidation treatments, are administered.

Supportive treatment. The therapeutic result of remission induction treatment hinges on the eradication of leukemic blasts. Most cytotoxic drugs that work effectively on malignant myeloid leukemic cells are also very toxic to normal hematopoietic precursor cells and the intestinal epithelium. Treatment with these agents therefore results in a long-term ‘aplastic phase’. This three-week long phase is associated with risks of infection, bleeding and anemia. Infections must be prevented if possible by giving the patient certain antibiotics and antifungal agents prophylactically, and nursing the patient in a low-germ environment. If an infection nonetheless occurs, this must immediately be treated with broad-spectrum antibiotics. If the number of thrombocytes falls to less than $10^9$/L, the occurrence of ‘spontaneous’ bleeding can usually be prevented by prophylactic administration of thrombocyte suspensions. Obviously, the hemoglobin level must also be maintained with erythrocyte concentrates.

Unfortunately, the remission of AML is rarely lasting. The average duration of complete remission is about 12 months. The median survival of patients achieving complete remission is 1.5-2 years. The prognosis decreases with increasing age. Patients over 60 years have the worst prognosis with the above treatment (only 10-15% alive after 2 years). Patients who do not achieve complete remission have a median survival of less than half a year. Patients who have indeed reached complete remission after the induction and consolidation treatment will need further treatment. AML patients with a good risk profile are given a third course of chemotherapy, while AML patients with a less good risk profile are eligible for allogeneic stem cell transplantation (alloSCT). In addition, patients who have reached morphological complete remission but in whom through more sensitive techniques such as flow cytometry or quantitative PCR, minimal residual disease can still be demonstrated, are eligible for alloSCT because they have an increased risk of relapse.

Stem cell transplantation. The goal of stem cell transplantation is to replace the malignant hematopoietic stem cells by normal hematopoietic stem cells, so that a new blood-forming system is created. In allogeneic stem cell transplantation, healthy stem cells from another person are used. Donors are usually brothers and sisters that are HLA-identical, sometimes fathers or mothers (haplo-identical) but nowadays
often HLA-compatible volunteers are used that have registered with one of the many donor stem cell banks. Another source of stem cells is umbilical cord blood. In autologous stem cell transplantation the stem cells are derived from the patient. The principle of the transfer of a limited number of stem cells to a recipient in order to restore normal hematopoiesis is only possible due to the pluripotent power of hematopoietic stem cells. Hematopoietic stem cells can be obtained by subcutaneous injection of hematopoietic growth factors (G-CSF), which leads to ‘mobilization’ of stem cells from the bone marrow into the blood. With the aid of leucapheresis technology, large quantities of stem cells can then be harvested from the blood. An alternative is the removal of bone marrow cells from the pelvis under general anaesthesia. Both methods provide sufficient stem cells that are excellent to use for transplantation. Nowadays, because of the higher yields resulting in a more rapid repopulation, the preference is for stem cells harvested from peripheral blood.

For the allogeneic stem cell transplant to succeed, the immunological response capacity of the recipient to the graft must be suppressed. This is done with the aid of a conditioning regime that consists, for example, of total body irradiation and a high dose of cytostatics. An additional advantage of this conditioning is that the underlying disease is eliminated as well as possible. Today so-called non-myeloablative conditioning is also frequently used. Here the emphasis is on suppressing the immune system and not so much the anti-leukemic effect. This conditioning is used particularly in patients with co-morbidity or that are older than 55-60 years. After conditioning, the stem cell suspension is administered via an infusion to the recipient. The stem cells migrate on their own to the then empty bone marrow spaces, settle there and begin to proliferate. The most important problems associated with allogeneic stem cell transplantation are the host-versus-graft reaction (transplant rejection), graft-versus-host-disease (‘rejection’ of the patient) and their complications, and long-lasting immunodeficiencies manifesting in viral and fungal infections. For patients with acute leukemia in remission who have an HLA-identical family donor or a well-matched unrelated donor and have not yet reached the age of 75 years, allogeneic stem cell transplantation, after myeloablative or non-myeloablative conditioning, increases the risk of long-term disease-free survival to 50-60%. Only in some of the allogeneically transplanted patients does acute leukemia recur (± 25-30%). The stronger anti-leukemia effect of donor stem cell transplantation is explained by an immunological graft-versus-leukemia effect of donor lymphocytes against (leukemic) cells of the patient.

The concept of allogeneic stem cell transplantation

The goal of alloSCT is to replace sick bone marrow with healthy donor’s bone marrow. Donor immune cells, particularly T lymphocytes, play a crucial role here. These T-lymphocytes recognize foreign peptides that are presented in HLA class I or II molecules. If these peptides are expressed only on hematopoietic cells, the graft-versus-leukemia effect (GVL) occurs. If these peptides also or only are expressed on healthy cells, graft-versus-host disease (GVHD) occurs. This is a potentially fatal condition that is treated with immunosuppressive drugs. In order to prevent GVHD, the transplantate can be depleted of T cells (T cell depletion). This clearly decreases the incidence and severity of GVHD. However, T cell depletion also results in more (viral) infections, and in a higher rate of relapses. In addition, frequently a low percentage of residual patient cells can be measured in the bone marrow compartment after alloSCT, so-called mixed chimerism. This is a consequence of the reduced allo-immune response caused by the T cell depletion. In order to try to reduce the recurrence rate, the donor T cells can be administered at a later time after the transplantation. In the LUMC, this donor lymphocyte infusion (DLI) is administered in patients with a poor risk profile 3 months after transplantation and in other patients after 6 months. The effect is measured in terms of the occurrence of the allo-immune response: the occurrence of GVHD and/or reduction of the percentage of patient cells in the bone marrow compartment. In patients with AML for whom a very sensitive measurable tumor marker is available (e.g. qPCR for t(8;21)), an alternative approach can be used by regularly measuring this marker after the alloSCT. If the marker becomes positive, DLI must be given, and the effect of the DLI can be assessed on
the basis of the tumor marker. The advantage of this approach is that patients that have no (molecular) recurrence of AML need not be unnecessarily treated with DLI, so that they are not exposed to the potential side effect of GVHD. The downside is that an AML recurrence can develop very rapidly, and that there is insufficient time available to administer the DLI and allow the allo-immune effect to emerge.

6.4.3 Chronic myeloid leukemia (CML)
Chronic myeloid leukemia (CML) is a malignancy of the pluripotent hematopoietic stem cell, which manifests primarily as a strong proliferation of myeloid precursor cells in the neutrophil series with normal maturation. The result is an increase in immature and above all mature cells from the granulocytic cells in the bone marrow and blood. There is virtually always an increase in eosinophilic and basophilic granulocytes. Sometimes thrombocytosis is seen. At the time of the diagnosis there have often already been months of symptoms such as fatigue, malaise, night sweats and weight loss. There is virtually always splenomegaly.

Incidence
The incidence is 1 - 1.5 per 100,000 people/year. The disease usually occurs between the 30th and 50th year of life.

Etiology and pathogenesis
The atomic bomb explosions in Japan made it clear that CML can be induced by radiation. The cause of cases occurring spontaneously in our country is unknown. In all cases, the Philadelphia chromosome is demonstrable either with cytogenetic or molecular techniques. This is an aberration in which there is a reciprocal translocation of chromosomal material from chromosome 22 to chromosome 9, and vice versa, and wherein the BCR and ABL genes are involved. This translocation occurs at the very early stem cell, and is therefore, in principle, present in all cell lines except in the T- and NK cells. This results in the production of a unique fusion gene product (protein). The importance of this translocation in the pathogenesis of CML was demonstrated in animals that developed a CML-like illness after being injected with the fusion protein or with cells transduced with the fusion gene.

Laboratory findings
The leukocyte count in the blood is greatly increased, often above 100x10^9/L, as a result of an increase in neutrophilic, basophilic and eosinophilic granulocytes. There is anemia in approximately 10% of the patients (normochromic, normocytic). An increase in granulopoiesis is seen in the bone marrow with a strong shift to the left and abnormal megakaryopoiesis. The Philadelphia chromosome (9;22) and/or the BCR/ABL fusion gene is demonstrable in all patients with cytogenetic analysis or molecular techniques.

Natural course
As long as maturation continues in CML, it is considered to be in the chronic phase. In some patients there is a transformation from the chronic to the acute phase (a maturation block develops). This usually takes place via an intermediate phase known as the accelerated phase. Hereafter, the patient’s remaining life can be limited to a few weeks during a transition to acute leukemia or a ‘blast crisis’, but it may also extend to more than a year during the more protracted ‘accelerated phase’. A blast crisis can be myeloid (see acute myeloid leukemia), or in 30% of cases, lymphatic, virtually always of the B-cell type. This is explained by the fact that the transformation occurs in a pluripotent stem cell.
For several years now, the disease in the chronic phase has been treated with tyrosine kinase inhibitors, which bind to the BCR/ABL protein product and thus inhibit its function thereof, so that the continuous proliferation of the malignant stem cell is blocked. With this ‘targeted therapy’, the prognosis is considerably improved in comparison with the time when patients were treated with cytostatics such as hydroxyurea, whether or not in combination with alpha-interferon. It would appear that in this way it is indeed possible that a number of patients are cured. Patients in whom the CML becomes resistant to tyrosine kinase inhibitors can be treated with an allogeneic stem cell transplantation. The accelerated phase or the blast crisis is treated as acute leukemia with a remission-induction and consolidation high-dose chemotherapy. Subsequently, an allogeneic stem cell transplantation is performed, since without transplantation these patients have a very poor prognosis. When a molecular relapse of the CML occurs a DLI containing allo-reactive donor T cells is administered, frequently restoring a complete molecular remission.

6.5 Malignant lymphatic disorders

6.5.1 Introduction
Malignant lymphatic diseases are often accompanied by lymph node enlargement. However, this is also common in non-malignant diseases. A differential diagnosis is given in Table 4.

Table 4. Differential diagnosis of lymph node swelling

<table>
<thead>
<tr>
<th>LOCAL</th>
<th>GENERALIZED</th>
</tr>
</thead>
<tbody>
<tr>
<td>• During a local inflammatory process</td>
<td>• In generalized infections</td>
</tr>
<tr>
<td>• Bacterial infections (including tonsillitis, skin infections, tuberculosis, syphilis, cat scratch disease, Yersinia)</td>
<td>• Bacterial infections (generalized dermatitis or furunculosis, brucellosis, tuberculosis, syphilis II, etc)</td>
</tr>
<tr>
<td>• Fungal or parasitic infections (toxoplasmosis)</td>
<td>• Viral infections (infectious mononucleosis, cytomegalovirus, rubella, measles, mumps, chickenpox, HIV)</td>
</tr>
<tr>
<td>• Sometimes with viral infections (infectious mononucleosis)</td>
<td>• In autoimmune diseases (SLE, rheumatoid arthritis)</td>
</tr>
<tr>
<td>• In sarcoidosis/M. Besnier-Boeck</td>
<td>• In sarcoidosis/M. Besnier-Boeck</td>
</tr>
<tr>
<td>• As a consequence of tumor</td>
<td>• With medications (hydantoin; rare)</td>
</tr>
<tr>
<td>• Hodgkin's and non-Hodgkin's lymphomas</td>
<td>• As a consequence of tumor</td>
</tr>
<tr>
<td>• Metastasis of breast, nasopharyngeal, lung and gastrointestinal carcinomas, melanoma etc.</td>
<td>• Non-Hodgkin's lymphoma, rarely Hodgkin’s disease, leukemia, especially CLL, sometimes also ALL and AML</td>
</tr>
</tbody>
</table>
Finally, the following rules of thumb apply:

- In children there is much more reactive than malignant swelling.
- In older people one must more quickly consider malignancy.
- A painless, firm swelling is more suspicious for malignancy than a painful swelling.
- Every persistent (generally > 6 weeks) lymph node enlargement for which based on history, physical examination, focal studies (ENT area) or serology there is no good explanation should be examined morphologically.

Malignant lymphatic diseases include the clonal abnormalities of B, T or NK cells. There are major differences in the maturation stage of the malignant cells at presentation. This explains the significant differences in microscopic picture, immunologic and genetic characteristics as well as clinical presentation, the clinical course, and the type of treatment. In the WHO classification the following sub classification is used: 1. Precursor lymphoid neoplasms involving either B or T lymphoblasts and clinically presenting as acute leukemia, 2. Mature B cell neoplasms, 3. Mature T-cell neoplasms and 4. Mature NK cell neoplasms, the latter three usually presenting clinically as malignant lymphoma.

Acute lymphocytic leukemia (ALL) is an overgrowth of immature lymphatic cells in the bone marrow, where they also belong under normal circumstances, with secondary spread into the bloodstream, lymph nodes, spleen, etc. In a malignant lymphoma (HL and NHL) the malignant lymphocytes accumulate in the lymphoid tissues, which fit their maturation or differentiation stage such as the thymus, lymph nodes, tonsils, spleen and MALT with possible secondary spread into the blood and bone marrow. Given the great diversity in normal B-and T-cell development and lymphoid tissues (think of the various lymphoid tissues including Mucosa Associated Lymphoid Tissue (MALT), and the different compartments in these tissues), it is not surprising that these malignancies are extremely diverse. Some mature lymphatic neoplasms are characterized by a high proliferation rate (aggressive lymphomas), others by a lack of apoptosis (indolent lymphomas). This determines not only the clinical course, but also the response to therapy. In addition to the histological picture, the immunological characteristics of B-and T-cells are also helpful for the determination of malignant lymphomas. An example of this is the appearance of immunoglobulins, and the immunoglobulin class switch during normal B-cell development and in B-cell leukemias and lymphomas. Cytogenetic abnormalities in the malignant cells are to an increasing extent of clinical significance. Often chromosome 14 is involved in a translocation, with a break point in the gene for the heavy chain of immunoglobulin in B cell lymphomas, and in the gene for the T cell receptor alpha in T cell lymphomas.

In Europe 80-90% of ALL, CLL and NHL, are of B-cell origin, the rest of T-cell origin (or rarely NK-cell origin). Since it has been known that the Reed-Sternberg cell, the malignant cell in classic Hodgkin's lymphoma, derives from the B lymphocyte, Hodgkin's lymphoma is now also definitively included in malignant lymphomas.

The expression of light and heavy chains in B cells can also be used to demonstrate the monoclonal character of a B-cell tumor: after all, tumor cells originate from a single cell in which the rearrangements of the immunoglobulin genes have already taken place. Through clonal expansion of these tumor stem cells, all daughter cells will also have the same gene rearrangements and express the same kappa or lambda light chains, which can be detected by DNA analysis. Furthermore, monoclonality can be traced by means of immunofluorescence in nearly all mature lymphoid malignancies of B cell origin, and it is a significant diagnostic criterion for malignancy in terms of reactive lymph node enlargement where the B cells are polyclonal.
6.5.2 Acute lymphocytic leukemia (ALL)
ALL is a proliferation of lymphoid precursor cells (lymphoblasts) in the bone marrow that spread through the bloodstream. The classification of acute lymphoblastic leukemia (ALL) is based primarily on immunological B- and T cell markers combined with cytogenetic characteristics. Patients with an ALL usually present, as with AML, with thrombocytopenia and granulocytopenia often in combination with anemia.

Incidence
ALL has an incidence of 1-2/100,000 persons/year. ALL is the most common malignancy in young children. In contrast to AML, there is no/hardly any increase with age.

Etiology and pathogenesis
Little is known about the etiology of ALL. Frequently there are characteristic genetic changes, particularly chromosomal translocations involving oncogenes and nuclear transcription factors. Deregulation of these genes or the formation of fusion-genes leads to disturbances in proliferation and differentiation. There are clear genetic differences between leukemia in children and adults. For example, in a quarter of the ALL cases in adults but rarely in children, there is a t(9;22) - the Philadelphia chromosome - which is also seen in CML. Some of these genetic aberrations are associated with relatively favorable or unfavorable behavior. Based on these and other parameters we then speak of ‘high risk’, ‘medium risk’ and ‘standard risk’ ALL.

Laboratory findings
Most patients present with thrombocytopenia, granulocytopenia, and anemia. In the bone marrow there are always numerous lymphoblasts, as is also the case in a blood smear. Sometimes the number of leukocytes (blasts) is extremely (> 100 x 10⁹/L) elevated. Using immunological marker studies it is possible to discriminate within the B-ALL’s the so-called common-ALL (cALL) that is entirely immunoglobulin negative from the somewhat more mature pre-B ALL with cytoplasmic expression of IgM. Both of these represent a proliferation of precursor B-cells that are still involved in immunoglobulin gene rearrangement and have a strong expression of CD10 on the cell membrane. This form is the most frequent (‘common’) (75%) in both children and adults. Finally there is T-ALL (10-15%), a leukemia of early T-cells that are still actively rearranging the T-cell receptor genes. It is sometimes difficult to establish a boundary between ALL and lymphoblastic lymphoma.

Natural course
As is the case with AML, the natural course of ALL is quickly infaust.

Treatment
The treatment of ALL consists of remission induction therapy, prophylactic treatment for the prevention of a leukemic localization in the central nervous system (CNS) and intensive consolidation and maintenance therapy.

Remission induction therapy: Combinations of vincristine, prednisone, an anthracycline and L-asparaginase induce a complete remission in approximately 90% of children with ALL and 70-80% of adults with ALL. This induction always involves the treatment of the CNS. In 5-10% of children and adults with ALL, the leukemia is already localised in the CNS (particularly in the meninges and the cerebrospinal fluid) at the time of first diagnosis. Much more frequently (up to + 50%), however, the leukemia recurs in the CNS during the period of hematological remission. To prevent recurrence in the CNS, in adults prophylactic intrathecal methotrexate injections are already given during...
remission induction, or immediately after the achievement of complete remission, either or not combined with cranial irradiation. In children, prophylactic intrathecal therapy is given as well, but radiation is only administered to children in the group of high risk patients who are not eligible for stem cell transplantation or have a clear CNS localization of their leukemia. This reduces the relapse percentage in the CNS to less than 10%.

Consolidation treatment: to consolidate the achieved complete remission, usually one or more intensive consolidation chemotherapy courses are given.

Maintenance treatment: usually long-term maintenance treatment is given, since otherwise relapse occurs generally within 2-3 months. The most common maintenance treatment consists of the oral administration of cytoxics (6-mercaptopurine and methotrexate). Maintenance therapy is usually continued until 1-3 years following the complete remission. The median survival time for children who achieve remission is >5 years (adult patients only 2.5 years).

Stem cell transplantation: in patients who at diagnosis already have a number of characteristics of a very aggressive course, allogeneic stem cell transplantation is performed.

6.5.3 Chronic lymphocytic leukemia (CLL)
CLL is classified by the WHO as a mature B cell neoplasm, and is characterized by an increase of small lymphocytes in the bone marrow and blood, lymph nodes, spleen and liver. As a result of an increasing bone marrow infiltration, over the course of years the production of normal blood elements becomes suppressed, leading to anemia, neutropenia and thrombocytopenia. However, the anemia can also be caused by auto-immune hemolytic anemia (AIHA) with positive direct antiglobulin test (IgG antibodies against erythrocytes). This is observed in approximately 5% of patients. Moderate thrombocytopenia (under 100x10⁹/L) is found in approximately 30%; in some cases this is due to autoantibodies against thrombocytes. Many patients with CLL initially have few or no symptoms, and the disease is often discovered ‘by chance’.

Incidence
CLL is the most common form of leukemia in the Western world. The incidence increases very sharply with age: under 50 years CLL is extremely rare, over 80 years the incidence is 80/100,000/year.

Etiology and pathogenesis
Not much is known about the etiology of CLL. Recently, it was discovered that the B cell receptor (BCR) of different CLL patients showed a high degree of similarity. A particular feature of these BCR’s involves the binding of an internal BCR-epitope by the heavy chain complementarity determining region. This binding induces continuous proliferation of B cells, finally resulting in the clinical picture of CLL. In addition, specific genetic changes (in chromosomes 11, 12, 13 and 17) have been described in CLL, which are of prognostic importance. Deletion chromosome 11q and deletion 17p are associated with a poor prognosis and deletion 13q with a relatively favourable prognosis. A characteristic property of CLL cells is not so much their increased proliferation, but rather inhibition of apoptosis resulting in a very slow accumulation of cells as a consequence of the significantly increased lifespan of tumor cells. Probably every patient with CLL has had a very long (a few years to decades) period of subclinical CLL before the diagnosis is made. In healthy older people, sometimes (3 -5%) by chance a small (<5x10⁹/L) population of B cells is found with the characteristics of CLL cells, monoclonal B cell lymphocytosis. Each year about 1% of these individuals develop CLL.
Laboratory findings

Often, the number of leukocytes (lymphocytes) is greatly increased. The number of peripheral granulocytes is at first usually normal. For the diagnosis of CLL, it is required that there are at least $5 \times 10^9/L$ monoclonal B-lymphocytes in the peripheral blood. Usually values are found between 20 and $100 \times 10^9/L$. Slight anemia (normochromic, normocytic) occurs in about half the cases. In the blood and bone marrow smear, there are many small lymphocytes, which damage easily when smears are made (‘Gumprechtse Schollen’). The tumor cells can be considered as the counterpart of a subgroup of normal, circulating B cells with weak expression of IgM and IgD on the cell surface and expression of the marker CD5.

Natural course

In general, CLL has a slow (indolent) course. There is a gradual and almost irreversible increase in tumor mass, whereby in one patient the infiltration in the bone marrow and blood is more prominent, and in another lymph node and spleen enlargement.

In 1975, Rai et al proposed a stage classification based on the clinical estimate of the tumor mass. This classification also has prognostic value.

Stage 0 includes patients in whom there is only lymphocytosis in the blood and in the bone marrow;
In stage I there are also enlarged glands;
In stage II, in addition to lymphocytosis there is also hepatosplenomegaly;
In stage III there is lymphocytosis with anemia (through displacement);
In stage IV there is thrombocytopenia (through displacement).

The median survival in stage 0 is longer than 150 months, in stage I approximately 100 months, in stage II 70 months, and in stages III and IV only 20 months. This means that a CLL patient of 70 years with stage 0 or I CLL statistically has a normal life expectancy.

During the course of the disease there may be a progressive decrease in the amount of normal immunoglobulins. In later stages of the disease, this humoral immune deficiency is causes death in approximately 50% of the patients due to an opportunistic infection. In the other 50%, resistance to chemotherapy with tumor progression will occur. Patients with CLL also have a greater risk of a second malignancy (carcinoma etc.).

Treatment

Most patients with CLL do not need immediate treatment, since the disease (a) is not curable and (b) can often remain indolent for a long time. That is why treatment only commences when there are general complaints or if a clear progression of the disease occurs (‘wait and see’ policy). Progress can manifest in increasing lymphocytosis, gland enlargement, hepatosplenomegaly, bone marrow insufficiency or autoimmune phenomena. The initial treatment usually consists of chemotherapy with fludarabin, cyclophosphamide and rituximab (a monoclonal anti-CD20 antibody) in fit, younger patients or chlorambucil plus rituximab in older patients. Treatment continues until the complaints disappear and the laboratory parameters of the blood or the size of the lymph nodes are normalised as much as possible. When ‘remission’ is achieved, the treatment can often be stopped and one can wait until progression occurs again. Local radiotherapy to glandular swellings causing complaints can be indicated in individual cases. Palliative blood transfusions may be administered. In case of hypogammaglobulinaemia and recurrent infections, immunoglobulins can be given. In addition to the clinical staging and the cytogenetic and molecular cell characteristics, the effect of the chemotherapy commenced is an important indicator for the prognosis. If a ‘remission’ is achieved, the median survival time is approximately ten years, while it is less than two years for patients who respond only moderately to treatment.
6.5.4 Hodgkin's lymphoma (HL)
Thomas Hodgkin described the disease later named after him for the first time in 1832. Later on, Reed and Sternberg described the giant cells typical of Hodgkin’s lymphoma (R-S cells). The precise nature of these RS cells was long uncertain, but it is now known that they involve lymphoid cells, nearly always of B-cell origin. For the Reed-Sternberg cells, the activation antigen CD30 is characteristic; however, they lack the ‘normal’ B-cell antigens (CD19, CD20). The diagnosis of Hodgkin's lymphoma is based on the presence of these RS cells in a typical background of many reactive cells including lymphocytes, histiocytes, eosinophilic and neutrophilic granulocytes. There is often a striking ring-shaped connective tissue reaction visible on microscopic evaluation, the ‘nodular sclerosis’. The diagnosis can be confirmed only with (immuno) histological examination. The WHO classification distinguishes two types: nodular lymphocyte predominant Hodgkin’s lymphoma (5%) and classic Hodgkin’s lymphoma (95%). In this syllabus we will hereafter limit ourselves to the classic form. In view of the need for finding often sporadically occurring R-S cells and the requirement to judge the surrounding cells, a large lymph node biopsy (preferably a lymph node excision, is necessary to establish a diagnosis.

In addition to the presence of RS cells, the clinical behavior is also characteristic and differs from non-Hodgkin's lymphomas: the disease almost always commences in one or more adjacent lymph nodes, virtually never extranodally, and spreads lymphogenically from lymph node to lymph node. For staging the Ann-Arbor system is used (see Table 5).

The disease usually presents with painless lymph node swelling. If more than one lymph node is affected, this often involves separately enlarged lymph nodes that feel solid (like ‘potatoes in a bag’). Frequently, the primary localizations are found in the cervical, supraclavicular and mediastinal lymph nodes. Especially mediastinal tumors can become very large and may give clinical symptoms, such as the vena cava superior syndrome.

The age distribution is also characteristic. The disease often affects young adults (15 -35 years) and a second peak occurs in the elderly (50-60 years).
Twenty to forty percent of the patients have B symptoms. These consist of fever, profuse night sweats or weight loss (more than 10% of body weight in 6 months). In some instances ‘alcohol pain’ is observed: pain in the area of the Hodgkin’s lesion immediately after drinking alcohol. Sometimes there is some fluctuation in the lymph node swelling or general symptoms. Fever may be of the Pel-Ebstein type: fever periods of one or two weeks, with a gradual increase and decrease, alternating with fever free periods of one to several weeks.

Incidence
In the Netherlands the incidence is about 3/100,000 people/year. In people that have had infectious mononucleosis, a higher incidence is seen.

Etiology and pathogenesis
The Epstein-Barr virus is associated with the pathogenesis of Hodgkin's lymphoma, but in only a minority of patients can the genome of this virus be demonstrated in the R-S cells. This probably involves a multi-step process in which abnormal, virus-infected cells are insufficiently eradicated by cytotoxic cells and a sort of symbiosis occurs between these cells and the surrounding T-cells. Eventual genetic changes in the R-S cells then lead to the formation of a neoplasm. The already mentioned background of reactive cells and fibrosis is caused by local production of numerous cytokines, such as Tumor Necrosis Factor (TNF) and interleukin-5. This means that the swelling of the lymph nodes is likely caused only to a very limited extent by the tumor cells but largely by the above-mentioned reactive ‘inflammatory’ cellular component.
**Laboratory findings**

Often few abnormalities are found. An elevated ESR is characteristic, and sometimes the alkaline phosphatase levels are elevated in the blood. Some patients have anemia, which need not always indicate bone marrow localization.

**Natural course**

Old literature from before 1960 shows that Hodgkin's lymphoma was a deadly disease resulting in death of the majority of patients approximately 5 years after diagnosis. This prognosis was significantly improved after the introduction of radiotherapy and (poly)chemotherapy.

**Treatment**

The choice of therapy depends on clinical stage. This principle has to do with the fact that the disease develops in one lymph node and subsequently spreads along lymphatic vessels. Comprehensive staging studies (Table 5) show that approximately 2/3 of the patients have localized disease (stage I, II) and only 1/3 a more disseminated form (st III, IV) (Table 6).

**Table 5. Diagnostic staging studies for Hodgkin’s and non-Hodgkin’s lymphoma (V: required, I: if indicated)**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate surgical biopsy: examination by an experienced pathologist</td>
<td>V</td>
</tr>
<tr>
<td>History: particularly note complaints about night sweats, fever and weight loss</td>
<td>V</td>
</tr>
<tr>
<td>Complete physical examination with special attention to the lymph nodes, Waldeyer ring (possibly ENT consult), liver and spleen size</td>
<td>V</td>
</tr>
<tr>
<td>Laboratory studies: BSE, hemoglobin, leukocyte count, leukocyte differentiation, platelet count, liver function (LDH), renal function, albumin</td>
<td>V</td>
</tr>
<tr>
<td>Imaging studies: Chest X-ray, CT neck/thorax/abdomen; PET scan</td>
<td>V</td>
</tr>
<tr>
<td>Crista biopsy (and possibly cytological bone marrow puncture)</td>
<td>V</td>
</tr>
<tr>
<td>Biopsy or fine needle aspiration of other suspicious lesions</td>
<td>I</td>
</tr>
</tbody>
</table>

**Stage I and II.** A differentiation is made between patients with limited Hodgkin’s with favourable prognosis (no B symptoms, younger than 50 years, normal BSE etc.) and patients with unfavourable symptoms (major localizations in the mediastinum, many affected glands, B symptoms etc.). The group with stage I or II disease can be cured with 3 to 4 courses of chemotherapy (depending on whether or not in the favourable prognostic group) followed by radiotherapy of the affected lymph nodes (so-called ‘Involved node’ irradiation). The standard chemotherapy treatment for all stages consists of a combination of adriamycin, bleomycin, vinblastin and dacarbazine (the ABVD schedule).

**Stage III and IV.** Patients with a disseminated form (stage III and IV) receive treatment with six to eight ABVD courses. This is only followed by radiotherapy to those lymph node stations that were very large (more than 5 cm diameter) at diagnosis or if the PET scan remains positive after the last chemotherapy.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of one lymph node station (I) or local extralymphatic spread (IE)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph node stations with or without local extralymphatic spread (IIE), all located on one side of the diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node stations on both sides of the diaphragm, with or without involvement of the spleen (IIIS) and/or local extralymphatic spread (IIIE, IIISE)</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse involvement of one or more extralymphatic organs or tissues with or without lymph node involvement</td>
</tr>
</tbody>
</table>

**General symptoms:**

A: asymptomatic  
B: if any one of the following symptoms are present:  
  - Unexplained fever above 38°C  
  - Unexplained weight loss of more than 10% in 6 months  
  - Profuse night sweats

The current treatment methods have led to a drastic improvement in the outlook of patients with Hodgkin's lymphoma. Cure is now possible for more than 90% of patients in stages I and IIA. For patients with disseminated forms this figure is 80%. The prognosis depends on obtaining complete remission after initial therapy. Patients without such a response have a much worse outlook and are eligible for intensive chemotherapy followed by autologous stem cell transplantation. Having a late recurrence (after more than 1 year), however, appears to have little effect on the course, and this recurrence can generally be treated successfully.
Table 7. Late complications as a consequence of radiotherapy and chemotherapy for Hodgkin’s or Non-Hodgkin’s lymphoma

<table>
<thead>
<tr>
<th>Chemotherapy related:</th>
<th>Radiotherapy related:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Secondary myelodysplasia/AML. Incidence from about one year after discontinuation of therapy, increasing to 4-6 years. After 10 years, the risk becomes very low.</td>
<td>- Carcinomas/sarcomas in previously irradiated area, for example lung and breast cancers after mantle field irradiation and tumors of the gastrointestinal tract after abdominal irradiation. Interval 10 to 20 years.</td>
</tr>
<tr>
<td>- Hormonal insufficiency. If women have premature menopause after treatment: oestrogen substitution in connection with risk of osteoporosis.</td>
<td>- Hypothyroidism after irradiation of the neck</td>
</tr>
<tr>
<td></td>
<td>- Coronary insufficiency/myocardial infarction after mediastinal irradiation</td>
</tr>
<tr>
<td></td>
<td>- Hyposplenism after splenic irradiation</td>
</tr>
</tbody>
</table>

| Possibly chemotherapy and radiotherapy related:                                      |
|-------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| - Non-Hodgkin’s lymphoma. Interval varies greatly, usually> 10 years.               |

| Advice relating to the monitoring of late complications, or active intervention:    |
|-------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| - Follow-up thyroid function and hormonal status                                    |
| - Blood pressure control, cholesterol/lipid spectrum control                       |
| - Anti-smoking policy                                                               |
| - Blood count monitoring (during the first 10 years)                                |
| - From 10 years after treatment: mammography, evaluation of digestive tract (if complaints), inspection of skin (carcinoma/melanoma) |
| - Pneumococcal vaccination, additional malaria prophylaxis                           |

| Preventive measures:                                                               |
|-------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| - Avoid excessive sunlight                                                          |
| - Information about self-examination: skin, breasts                                 |
| - Advice on cardiovascular disease risk: stop smoking, avoid excessive alcohol etc. |

Complications and late sequelae of therapy: (Table 7)

Early toxicity: this is the same as with other forms of chemotherapy and irradiation. Fatigue and nausea are in the foreground. Sometimes lung toxicity occurs (starts with dry cough) due to the bleomycin. Safe contraception must be used during treatment. After treatment with ABVD, pregnancy is quite possible and there are insufficient arguments, including in terms of the foetus, to advise a man or woman in remission against pregnancy. In general, premature menopause due to ABVD chemotherapy does not occur, but if it does hormonal substitution should be done to prevent osteoporosis.

Late toxicity: radiotherapy to the mediastinum can lead to heart damage after several years, expressed in an increased risk for coronary sclerosis, particularly in patients with other risk factors (smoking, hypertension, hypercholesterolemia). Secondary malignancies occur after both treatment modalities. After chemotherapy, this concerns mainly myelodysplasia that quickly turns into acute myeloid leukemia. At the sites of radiotherapy it involves mainly solid tumors, such as breast cancer and lung cancer (smoking!). The incidence of heart failure and solid tumors increases over time. Therefore, lifelong follow-up is necessary for all patients with Hodgkin's and non-Hodgkin's lymphoma so that these late consequences of therapy can also be identified in good
time. With these long term follow-up data new therapeutic modalities can continue to be developed that are just as effective but less toxic.

6.5.5 Non-Hodgkin's lymphomas (NHL)
Unlike Hodgkin's lymphomas, non-Hodgkin's lymphomas form a very heterogeneous group of lymphoproliferative diseases. The WHO classification distinguishes many different types mainly differing in biological characteristics (morphology/histology, immunophenotyping, cytogentic and molecular techniques). The clinical course and prognosis can often be determined from these biological properties. Regarding the clinical course, NHL are divided in aggressive and indolent types. This heterogeneity can be understood considering the great diversity of normal B-and T-cell development and the histological complexity of normal lymphoid tissues. In addition to the differences in histological and immunophenotypical characteristics there are also differences in the tumor cell spread (see below pathogenesis).

In 60% of patients with NHL, the first complaint is enlargement of the lymph nodes. This is called a primary nodal NHL. Lymphadenopathy can occur both in a localised and generalised way. On physical examination, the lymph nodes are usually not painful, can be well demarcated and are rubbery in consistency. Lymph node enlargement can also occur inside the thorax or the abdomen, with complaints only occurring at a later point. Sometimes there is ascites or pleural fluid due to the disruption of lymphatic drainage in the lymph nodes.

In 40% of patients, there are extranodal presentations such as in the tonsil, nose (sinuses), stomach, small intestine, lung, but also elsewhere (skin, brains, bone, thyroid gland all the way to the heart). NHL from the stomach, intestine, salivary gland and lung probably comes from MALT. The symptoms of this extranodal NHL are very diverse and depend on the localization (e.g. symptoms consistent with an ulcer with a gastric lymphoma, headache and epilepsy in primary lymphoma of the brain, etc.).

An essential difference in comparison with Hodgkin’s lymphoma is that NHL spreads predominantly hematogenically (intercity train behavior) and to a lesser degree lymphogenically. The distribution of the involved lymph nodes throughout the body is much more dispersed in NHL compared to HL, where neighbouring lymph nodes become increasingly involved. With modern and highly sensitive detection methods such as polymerase chain reaction (PCR), tumor cells circulating in the blood can almost always be identified.

This hematogenous spread can cause swelling of lymph nodes in both the neck and groin without involvement of intermediate lymph node stations. Many of the patients have splenomegaly. Bone marrow and liver localization are frequently encountered.

Staging is performed using the Ann Arbor classification (see Table 5 and 6). The results of the staging studies in NHL show that more than 80% of patients present with disseminated disease (stage III, IV). This is in contrast to HL where the majority of patients presents with limited stage I or II. The greatest significance of staging for NHL is to identify the rarely occurring stage I, because in these patients cure after radiotherapy and/or chemotherapy can be achieved much more easily than in stage II-IV.

Incidence
Each year the diagnosis of non-Hodgkin's lymphoma is made in 12 people per 100,000 inhabitants in the Netherlands. Incidence increases sharply with age: the median age is> 65 years. For such reasons as ‘greying’, there is a clear increase in the incidence of NHL in Western countries (approximately 5% per year).
Etiology and pathogenesis

In some autoimmune diseases (Sjögren's syndrome in particular, to a lesser extent rheumatoid arthritis, celiac disease, Hashimoto's disease), a predisposition to NHL is described. This may be based on chronic stimulation of the immune system. Primary malignant lymphoma of the stomach is also caused by chronic immune stimulation. The hypothesis is that some patients with an H. pylori infection of the stomach develop chronic gastritis, whereby eventually in the mucosa, mucosa associated lymphoid tissue (MALT) is induced (in contrast to the small intestine, the stomach lacks MALT). Through years of exposure under the influence of bacteria, finally one clone of B cells with genetic deviations, and thus malignant lymphoma, will be formed. The role of this bacterium is plausible because the removal of the stimulus (eradication of the bacteria with antibiotics) leads in some patients to tumor reduction and even recovery. Increased frequency of NHL is also observed in some forms of primary and secondary immune deficiency. An example is the increased incidence of Burkitt lymphoma associated with Epstein-Barr virus (EBV) infection in equatorial Africa. Here malaria and parasitic infections are endemic and can lead to immune deficiency. Whereas in normal individuals EBV-infected cells are killed immediately by cytotoxic T-cells, in immune-deficient individuals these cells survive and can acquire additional mutations finally resulting immortalised EBV infected B cells. Continuing proliferation finally results in Burkitt lymphoma. Patients who receive immunosuppressants (such as after renal transplant), or have received chemotherapy years ago for another malignity, have a somewhat increased risk of NHL. The etiology of most NHLs, however, is not known.

As is the case in AML and ALL, in many NHLs specific chromosomal translocations can occur, resulting in activation of, for example, dominant oncogenes. Examples are the t(8;14) with MYC activation in Burkitt lymphoma, the t(14;18) with BCL-2 activation in follicular lymphoma and the t(11:14) with activation of Cyclin D1 in mantle cell lymphoma. These oncogenes play a role in the regulation of cell division and cell survival (apoptosis) of normal cells, and play an essential role in the multi-step pathogenesis of these lymphomas.

Laboratory findings

The findings are very diverse, depending on the nature of the NHL (T-versus B-cell type, proliferation or apoptosis inhibition), the manner of dissemination (hematogenously versus lymphogenically), the extensiveness (bone marrow, liver), etc. As already pointed out NHL can be leukemic with lymphocytosis in the blood and in the bone marrow. In some cases, the tumor cells secrete monoclonal immunoglobulin (M-protein). Elevation of LDH is especially seen during high cell turnover and is an important prognostic parameter.

Natural course

The natural course of NHL is very diverse and highly dependent on the degree of proliferation or apoptosis inhibition. For example, NHLs with apoptosis inhibition have an indolent course that hardly changes in response to therapy (median survival 5-7 years); in patients with highly proliferating lymphoma the natural course is aggressive. Without therapy, they will virtually all have died within a few months/years or weeks/months. On the other hand, these lymphomas are particularly sensitive to therapy and patients can be cured.

Treatment

Despite the fact that there are many different types of lymphoma it is not so that each type has its own treatment. In general the type treatment depends on whether the lymphoma is of indolent or aggressive nature. The following guidelines have been established. Indolent lymphomas; example: follicular lymphoma.
The second common B-NHL: 25% of all B-NHL. These types are characterized by a prolonged course with repeated recurrences after radiotherapy or chemotherapy and a minimal chance of cure. In stage I or limited II, radiotherapy is the first choice. Chemotherapy, in combination with rituximab (anti-CD20), is preferred in disseminated disease. The result is mainly palliative: a mortality rate of 15% per year has been established, irrespective of the type of treatment. Many centres therefore have an even more cautious approach in the disseminated stages of the disease and treat only when symptoms such as anemia, thrombocytopenia, organ involvement, e.g. renal failure occur (‘wait and see’). In the course of follicular lymphoma, in approximately 50% of cases, independently of the therapy, a secondary transformation to an aggressive lymphoma occurs. From that point onward the prognosis becomes worse.

Aggressive lymphomas; example: diffuse large B-cell lymphoma. These are most common: ± 35% of the B-NHL. Cure of the patient is the treatment goal. In localized stage I, combined chemo- and radiation therapy is used. Patients with stage II, III or IV, and patients with recurrence after radiotherapy for stage I, receive chemotherapy combined with rituximab. A frequently used combination of chemotherapy is that of cyclophosphamide, adriamycin (also named doxorubicin), vincristine and prednisone (CHOP). Six to eight courses are given to obtain a complete remission. Often bulky (large) localisations of the NHL receive additional irradiation. The treatment results depend on the presence of various prognostic factors (see below). Approximately 60-70% of patients achieve complete remission with rituximab-CHOP, but in half of the patients there will be relapse within 3-5 years. These patients are then eligible for intensive therapy with autologous stem cell transplantation. This salvage therapy results in cure in approximately 50% of patients.

Prognostic factors
The behavior of the NHL and its response to therapy is highly dependent on the histological classification and stage at presentation. Some general parameters have also been identified as prognostic factors, such as: LDH, bulky disease (lymphoma larger than 5 cm), age, performance status and number of extranodal localizations.
For follicular lymphoma, the FLIPI score (Follicular Lymphoma International Prognostic Index) is used:

<table>
<thead>
<tr>
<th>RISK FACTORS (1 point for each risk factor)</th>
<th>PROGNOSIS (Survival rate 10 years after diagnosis):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 yrs</td>
<td>FLIPI 0-1/5: 70%</td>
</tr>
<tr>
<td>Hemoglobin &lt; 7.4 mmol/L</td>
<td>FLIPI 2/5: 50%</td>
</tr>
<tr>
<td>Ann Arbor stage III-IV</td>
<td>FLIPI 3-5/5: 35%</td>
</tr>
<tr>
<td>LDH increased</td>
<td></td>
</tr>
<tr>
<td>Lymph node regions &gt;4</td>
<td></td>
</tr>
</tbody>
</table>
For diffuse large-cell B NHL, the IPI-score is used:

**RISK FACTORS (1 point for each risk factor)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>Overall score according to WHO</td>
<td>&gt; 1</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td>III - IV</td>
</tr>
<tr>
<td>LDH before starting treatment</td>
<td>increased</td>
</tr>
<tr>
<td>Extranodal localizations</td>
<td>&gt; 1</td>
</tr>
</tbody>
</table>

**PROGNOSIS (chance of long-term survival with anthracycline/rituximab-containing standard treatment)**

<table>
<thead>
<tr>
<th>IPI</th>
<th>Chance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/5</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>1-2/5</td>
<td>70-90%</td>
</tr>
<tr>
<td>3-5/5</td>
<td>40-70%</td>
</tr>
</tbody>
</table>