MALIGNANT LYMPHOMA DURING CHILDHOOD AND ADOLESCENCE

IMPLICATIONS FOR ORAL HEALTH IN LONG-TERM SURVIVORS

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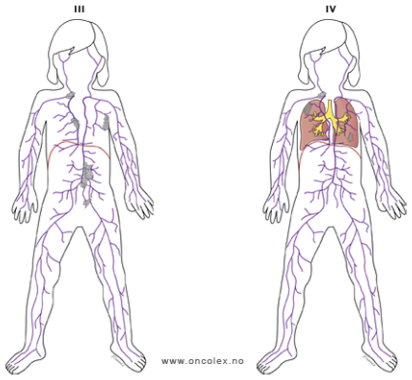

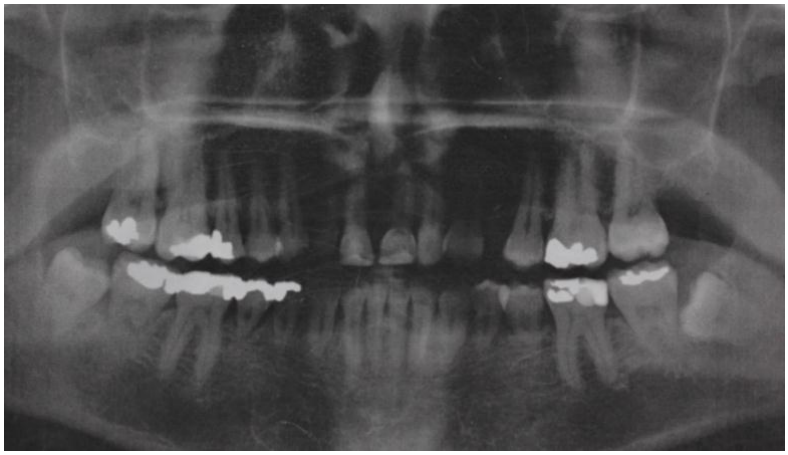

Supervisors:
Associate professor Bente Brokstad Herlofson
PhD candidate Petter Wilberg

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Forord

Denne oppgaven er en del av et stort samarbeidsprosjekt mellom Oslo Universitetssykehus (Radiumhospitalet) , Oslo Universitetssykehus (Rikshospitalet) og Det odontologiske fakultet, Universitetet i Oslo. Prosjektet har som mål å undersøke senkomplikasjoner hos overlevere etter akutt lymfatisk leukemi, malignt lymfom og germinalcelle-cancer behandlet i barnealder. Prosjektet har i sin helhet etisk godkjenning av REK [1].

Vi presenterer i dette dokumentet en litteraturgjennomgang av maligne lymfomer og hvordan disse påvirker munnhulen og dens strukturer, men vårt prosjekt hadde tre ulike faser som også inkluderte en klinisk studie:

1. Første fase var planlegging og utarbeidelse av en prosjektbeskrivelse for studentstipendiatsperioden. Dette inkluderte en gjennomgang av litteraturen relatert til maligne lymfomer og oral helse spesielt og maligne tilstander generelt. Denne litteraturgjennomgangen ble brukt som bakgrunn for det vidre arbeidet i den praktiske delen av arbeidet.
2. Andre fase var praktisk. Vi ble sommeren 2011 tildelt forskningsstipend fra NFR knyttet opp mot en praktisk del av prosjektet. Dette arbeidet gikk ut på å måle rot-krone ratio på premolarer og molarer på 112 OPGer for å undersøke om behandling av malignt lymfom i barne- og ungdomsalder påvirker tannutviklingen. Metoden som ble valgt er beskrevet av Höllta og medarbeidere i 2004 [2]. Dette viste seg å være et svært omfattende og tidkrevende arbeid og det ble dessverre ikke tid til å inkludere resultatene fra den praktiske delen i denne oppgaven. Det er en likevel en målsetning at noen av de preliminære resultatene vil være klare for presentasjon ved fremføringen av oppgaven. Det er også et mål at de bearbeidede resultatene kan inngå i en artikkel om oral helse hos langtidsoverlevere etter behandling av malignt lymfom knyttet til doktorgradsprosjektet til stipendiat Petter Wilberg.
3. Tredje fase var bearbeiding av litteraturen og målingene vi hadde gjort. Alle målingene fra det praktiske arbeidet ble lagt over i SPSS for analyse. Denne fasen inkluderte også utarbeidelsen av dette dokumentet. Det viste seg på slutten at det ikke var tid til en presentasjon av den praktiske delen av arbeidet på en måte som kunne yte alt arbeidet rettferdighet. Vi valgte derfor å kutte den delen for å konsentrere oss om en presentasjon av bakgrunnen for det arbeidet vi har utført.

Arbeidet er utført av stud. odont. Lobna Ed-Dahbi og Zhenya Draganova (kull H-07).

Vi ønsker å takke Bente Brokstad Herlofson og Petter Wilberg for all hjelp vi har fått i forbindelse med oppgaven vår.

Introduction

Cancer in general

According to the Cancer register of Norway the number of new cancer cases diagnosed each year is rising. In 2009, a total of 27 520 new cases of cancer were recorded in Norway, out of which 14 792 occurred in men and 12 728 in women [3].

Increasing numbers of breast cancer in women, and lung and colorectal cancer in both sexes shows a true rise of these types of cancer in the Norwegian population. On the other hand, higher cancer incidence may be a result of people living longer or that diagnostic procedures in medicine have improved over the last decade [3].

Childhood cancer

Each year, there is between 120 and 150 new cases of childhood cancer in Norway. These make up for approximately 0, 6% of all cancer incidence in the population [3].

From 01.01.1985 until 31.12.2009 there were 3622 new registered cases of children with cancer in Norway. This included children under the age of 15 [4].

Malignant lymphoma (ML) is the third most common childhood cancer type in Norway after tumors of the CNS and leukemia. It is divided in two forms: Non-Hodgkin`s lymphoma (NHL) and Hodgkin`s lymphoma (HL). In 2009, 16 out of 780 cases of ML occurred in children (12/423 in males and 4/357 in females) [3].

Incidence of childhood cancer in Norway for the period 1985-2009 is stable [4]. On the other hand, the 10-year-survival rate after cancer treatment in children has increased during the last decades to over 80% for patients with Non- Hodgkin`s lymphoma and over 90% for patients with Hodgkin`s lymphoma . There is no significant difference in survival rates between different regions in Norway. This indicates that children with cancer receive the same good treatment [4]. Nevertheless, new data show a higher risk for late complications in these patients than in healthy Norwegians. After cancer treatment they are followed in pediatric hospitals departments until they are 18 years, and then at their general medical practitioners for the rest of their life as “healthy” cancer survivors [3].

Malignant lymphoma

Classification

Malignant lymphoma (ML) affects the lymphatic system and is a heterogeneous group of diseases which can be classified into 2 main groups: Hodgkin`s lymphoma (HL) and non-Hodgkin`s lymphoma (NHL). They differ in how they behave, spread, and respond to treatment [5].

Hodgkin`s lymphoma

HL constitutes 30-40% of all lymphomas. It can be classified in two groups: Classical HL and Nodular lymphocyte- predominant HL [6].

HL originates from malignant transformation of lymphocytes, most often in B-cells. Typical localization for this type of cancer is the lymph nodes and the spleen. Lymphomas are categorized by their size, shape, and growth pattern microscopically [6].

HL in adults and children share some biological aspects. Reed-Sternberg cells and big Hodgkin`s cells are distinctive for the inflammatory environment in HL. They seem to be resistant to apoptotic stimuli and are essential for the diagnosis of classical HL [6].

Non-Hodgkin`s lymphoma

NHL accounts for almost 60% of all lymphomas and can be classified as non- B-cell lymphoma, B-cell lymphoma, and large cell anaplastic lymphoma [6].

NHL is a systemic type of cancer which originates in lymphocytes all over the human body. NHL in children is more aggressive and diffuse than NHL in adults. In addition it often involves extranodal locations [6].

The differences between NHL in adults and children are:

- Lymphoma in children is a high grade malignant lymphoma. It tends to grow sporadic, which means the cancer cells infiltrate the tissue without setting any distinct boundaries [6].
- A large portion of childhood-lymphoma is initially extra-nodal. This means that children lymphomas occur in other sites, apart from lymph nodes, such as in the gastro-intestinal tract, tonsils, liver, spleen, thymus, and skeleton. A typical site for NHL in the head region is the Waldeyer`s ring [5]. Waldeyer`s ring is:”an anathomical term describing the lymphoid tissue ring located in the pharynx and to

the back of the oral cavity. The ring consists of pharyngeal tonsil, tubal tonsil, palatine tonsils and lingual tonsils" [7].

- It is fast- growing and very seldom chronic in children [6].

Incidence

The cancer incidence in Norway has increased since registration of new cases in the Cancer register started in 1952. Whereas the incidence of childhood cancer has risen in many countries over the last decades, such a rise has not been detected in Norway [3].

The incidence of HL shows two peaks in the onset of disease; one in early age and one later in life. It is very rare in children under the age of 5, and is affecting boys more often than girls. Incidence for NHL increases continuously throughout life and affects boys more often than girls [6].

Number of new cases by primary site and sex for 2009:

HL:	male -78	female -44	total -122
NHL:	male -483	female -404	total -887 [3]

Number of new cases by primary site and sex for 2000:

HL:	male -64	female -64	total -128
NHL:	male -385	female -323	total -708 [3]

Average annual number of new cases by primary site in children of age 0-14 for the period 2005-2009:

HL:	boys -5	girls -1	total -6
NHL:	boys -5	girls -3	total -8 [3]

The incidence of malignant lymphoma (ML):

ML was the 4th most common type of cancer among Norwegian boys between 0-14 years and the 6th most common in girls during the period 2005-2009 [3].

According to the Cancer Registry males develop malignant lymphoma more often than females. There has been a small change in this relationship for HL over the last decades. The male/female ratio for HL was 1, 6 for the period 1978-1982 and 1, 4 for the period 2005-2009. For NHL the male/female ratio was 1, 4 for the period of 1978-1982 and 1, 4 for the period of 2005-2009 [3].

Etiology

For most cases of ML the etiology is unknown. It is believed that risk factors for adults can be assessed as risk factors for children as well [6]. The most common risk factors are:

Weakened immune system

- Individuals with immune defects or undergoing treatment with immunosuppressive drugs are proven to be at risk [6]
- HIV/AIDS patients [6]

Epstein-Barr virus

The relationship between the virus and lymphoma is not perfectly clear but in some individuals with HL the virus can be detected in big Hodgkin and Reed-Sternberg cells. It is unknown how the virus may affect cancer progression. Burkitt`s lymphoma is often encountered in Africa in regions severely affected by malaria. It makes up for 50% of all childhood cancer in these regions. Malignant cells in these cases are always infected with Epstein-Barr virus. It is believed that interaction between chronic malaria infection and infection with Epstein-Barr virus can result in formation of a cancer cell. Epstein-Barr virus is also believed to play a role in lymphoma formation in immunosuppressed or HIV patients [6].

Cancer therapy

NHL has occurred as a secondary cancer after treatment of HL with chemotherapy alone, or in combination with radiotherapy. Almost 5% of adults who have been treated for HL develop NHL later in life. This risk seems to be lower for children [6].

Inheritance

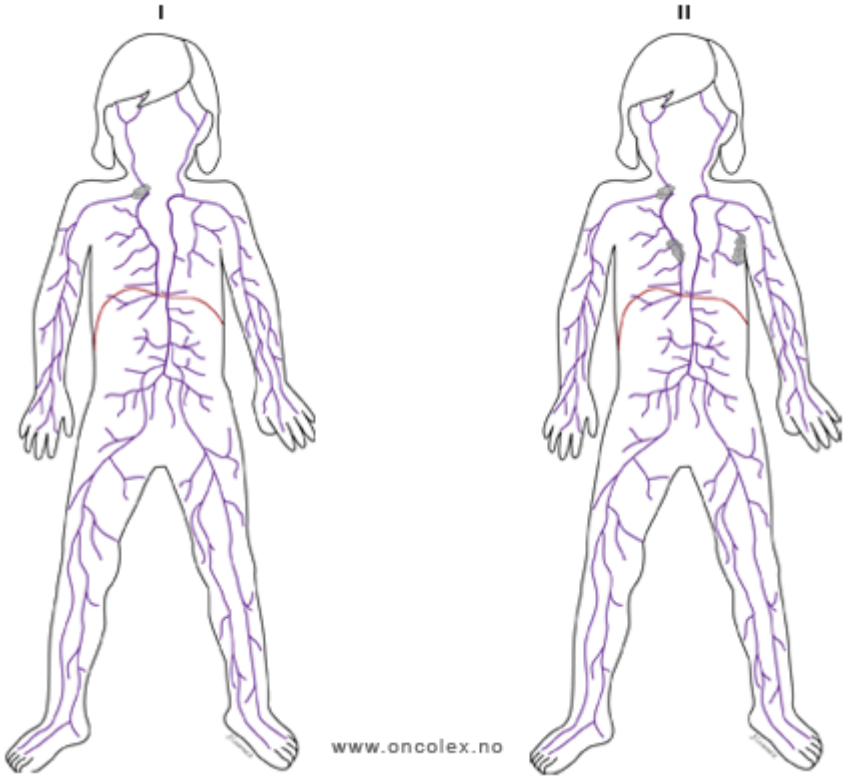
There is no clear relation between HL and specific genes, even though it seems to be a link with some HLA-antigens. There is a statistical data showing almost 50% higher risk of HL in children of parents who have had HL [6].

Stages

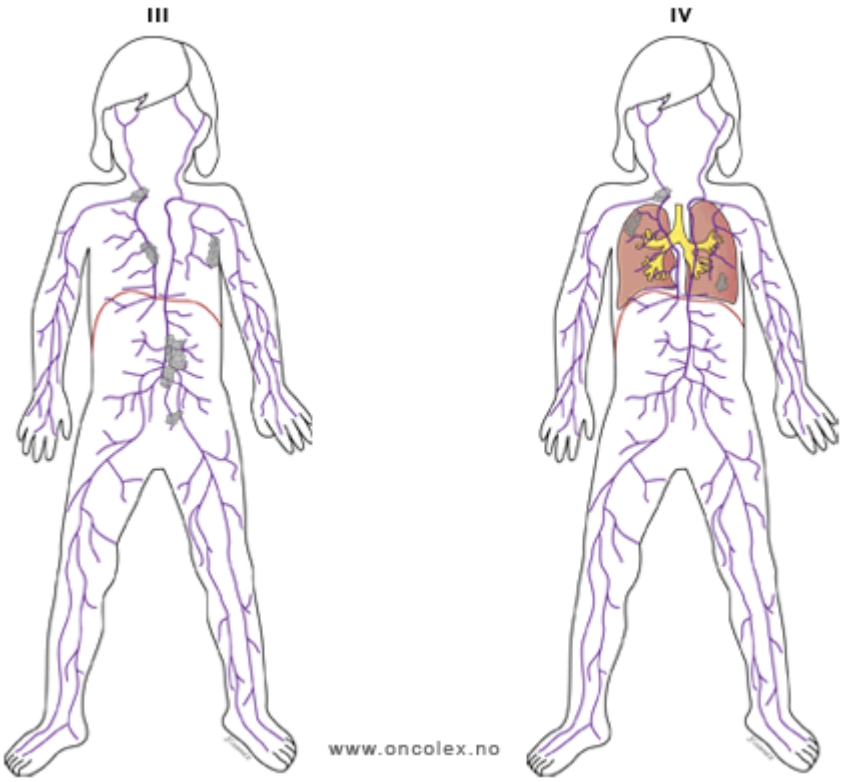
Staging is important when medical staff have to choose the right treatment and assess the prognosis of each patient [8].

Hodgkin`s lymphoma

The Ann Arbor classification is the system most commonly used [8].



Stage 1: Involvement of a single LN region or of a single extranodal organ or site	Stage 2: Involvement of two or more LN regions on the same side of the diaphragm, or localized involvement of an extranodal organ or site



Stage3: Involvement of LN regions on both sides of the diaphragm

Stage 4: Diffuse or disseminated disease in one more extra lymphatic organs or tissues with or without affection of LN.

Patients can be subdivided into two groups:

Group A: Patients who do not have general symptoms.

Group B: Patients that have one or more of the general symptoms:

- Unaccountable weight loss of over 10% in the last 6 months
- Unaccountable persistent fever (temperature over 38 grades) for the last month
- Repeated night sweating for the last month [6].

Non-Hodgkin`s lymphoma

St. Jude's staging system for pediatric non-Hodgkin's lymphoma	
Stage I	A single tumor (extranodal) or single anatomic area (nodal) with the exclusion of the mediastinum or abdomen
Stage II	A single tumor (extranodal) with regional node involvement Two or more nodal areas on same side of diaphragm Two single (extranodal) tumors with or without regional node involvement on same side of diaphragm A primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only, grossly completely resected
Stage III	Two single tumors (extranodal) on opposite sides of diaphragm Two or more nodal areas above or below diaphragm All primary intrathoracic tumors (mediastinal, pleural, and thymic) All extensive primary intra-abdominal disease, unresectable All paraspinal or epidural tumors, regardless of other tumor sites Multifocal bone (now considered stage III rather than IV)
Stage IV	Any of the above with initial central nervous system and/or bone marrow involvement

Intensity and length of the treatment vary accordingly to stage and prognosis.

Spreading pattern

Both HL and NHL are diseases which occur inside the lymphatic system. Lymphomas are commonly localized in lymph nodes, thymus, and spleen. Since almost all organs have lymphatic tissue, lymphomas can occur almost everywhere in the human body; i.e. in intestines, skin, and the skeleton [6].

Lymphomas can spread either via the lymphatic or the blood system [6].

Treatment

Treatment of NHL and HL depend on type and stage of the lymphoma. Different protocols are used.

Treatment of HL

The most widely used protocol in Norway for treating HL is GPOH-HD-95. This is a protocol used in an international collaboration study in which Norway participates. The protocol, with the latest updates, constitutes the standard treatment of HL in Norway nowadays. The treatment of HL is conducted in regional hospitals, or under their supervision.

It involves chemotherapy for all patients , and post- radiotherapy for most of the patients. Patients are stratified in different therapy groups by staging of their disease. Therapy group 1 is for early stage of the disease, group 2 – for intermediary, and stage 3- for advanced stage of the disease [6].

Medical treatment: Cytotoxic drugs are used as the main treatment of childhood lymphomas. A combination of 4 different cytostatica is the common regime. The most used drugs are cyklofosfamid, vinblastin, dakarbazin and bleomycin. They all act by attacking fast dividing cells [9].

Surgery: Biopsy is a standard procedure for complete typing of the lymphoma. Surgery is usually not used for treatment [6].

Radiotherapy: Radiotherapy is usually part of the treatment of HL. Total body irradiation is usually part of the treatment together and after stem cell transplantation [6].

In patients with HL, radiotherapy increases the chance for long term survival. However, there is a risk for late term complications in children who undergo radiotherapy. These are growth disturbances, damage of the irradiated organs and irradiation- based secondary cancer [6].

Treatment of NHL

In NHL treatment has improved greatly in the last ten years and there are three main treatment protocols. One of the most important reasons for this improvement is the use of intensive combination of different group of drugs as a primary treatment of the patients. Before 1971, only few of the children who received the diagnosis NHL lived for more than 5 years. All of them had localized disease. Surgery and radiotherapy was used for treatment of stage 1 and 2 patients, but 2/3 of them had relapsed. Today, chemotherapy is the first choice of treatment for all types and stages of NHL in children [6].

Surgery: There are a few, uncommon, indications for surgery in NHL, one such is tumor affecting the parotid gland [10].

Medical treatment: Usually the same cytotoxic drugs as used in the treatment of HL [9].

Radiotherapy: Used as a primary treatment of children with NHL in cases when CNS is primary affected in non-B cell lymphoma. The amount of absorbed radiation is measured in Gray (Gy). Children under the age of 5 in this group receive 18 Gy to the head region. The daily dosage is 1, 5 Gy. It is given in 5 fractions per week, until the total dosage is reached [6].

Survival rates

The relative survival rate is "a way of comparing survival of people who have a specific disease with those who do not. The percentage of survivors is usually determined at specific times, such as two years and five years after diagnosis or treatment. The survival rate shows whether the disease shortens life" [11].

The survival rate for both NHL and HL has been steadily increasing over the last decades. The following data about incidence, male/female ratio, and survival rate are extracted from the Cancer Register of Norway [3].

Hodgkin`s lymphoma:

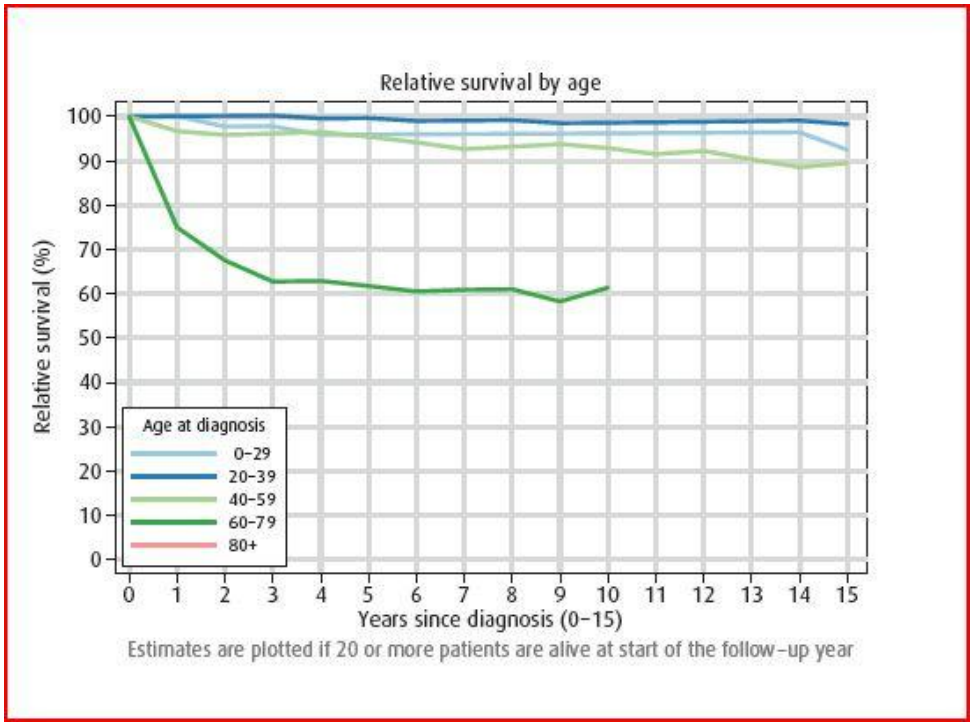
Survival	Males (%)	Females (%)
1 year	91,8	93.3
5 years	88,8	90,6
10 years	87,0	92,9
15 years	88,3	90,7

Non-Hodgkin`s lymphoma:

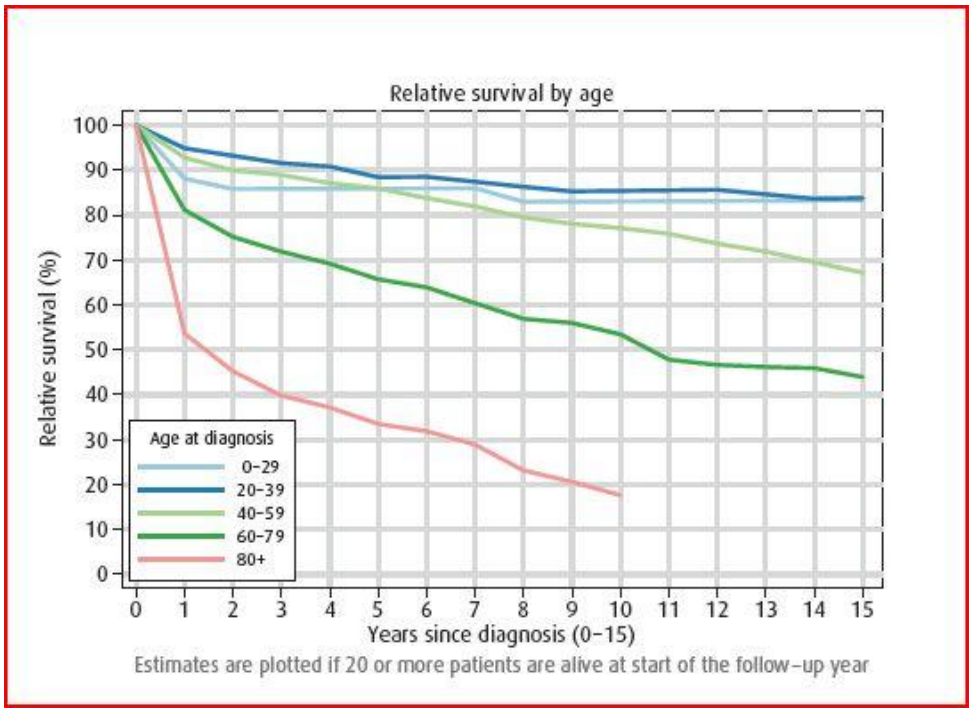
Survival	Males (%)	Females (%)
1 year	79,2	82,4
5 years	68,6	71,2
10 years	61,5	65,8
15 years	55,2	64,6

Relative survival (RS) up to 15 years after diagnosis by sex and age (2007–9):

Hodgkin`s lymphoma (ICD-10 C81) [3]:



Non-Hodgkin lymphoma (ICD-10 C82–85, C96) [3]:



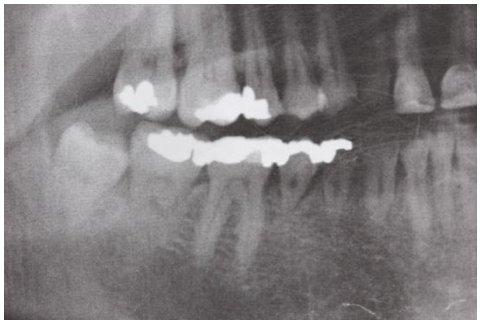
Oral complications

Anticancer therapy and tooth formation and development

Anticancer treatment in children is known to cause both acute and chronic longterm oral complications. It includes treatment with both radiotherapy and cytotoxic drugs of children while tooth formation is ongoing [12].

“Acute complications such as mucositis, xerostomia, bleeding, and infections occur three times more commonly in children than adults”. “The mouth is been documented as the most common source of sepsis in immunosuppressed patients with cancer” [13].

Some of the most common complications are foreshortening and blunting of roots, incomplete calcification, premature closure of apices, delayed or arrested tooth development, and caries [12]. Osteoradionecrosis can occur after extraction or surgery in patients who received radiotherapy in head and neck region. The mandible is more prediposed than the maxilla [13].



Male long-term Hodgkin`s disease survivor, treated with radiation at the age of 8 years.

Tooth formation and development

Tooth development starts between the sixth and eighth week of embryogenesis from embryonic cells and can be divided into 4 stages:

Bud stage: In each dental arch a dental lamina forms along with 10 buds. These 10 buds will mature to 10 deciduous teeth. Ectomesenchymal cells surround the bud [14].

Cap stage: Each tooth bud grows around an ectomesenchymal aggregation to an enamel organ. Dental papilla and dental follicle are other structures you can see at this stage. The enamel organ will generate enamel and dental papilla will generate dentin and pulp while the dental follicle will generate periodontal structures which support the teeth [14].

Bell stage: Bone starts to form. Meckels cartilage is visible. On the periphery of the enamel organ you can divide the cells into 4 layers. From outer to inner layer; outer enamel

epithelium, stellate reticulum, stratum intermedium and inner enamel epithelium. Development of the crown will start at this stage. Other important structures are enamel knots and enamel cord [14].

Crown stage: Hard tissue like crown and dentin starts forming [14].

Amelogenesis

It starts during the late bell stage. The enamel formation goes through a secretory stage and a maturation stage [14].

Mesenchymal cells differentiate to odontoblasts (OB) which produce predentin. When predentin undergoes mineralization, cells in the inner enamel epithelium will transform to ameloblasts which produce enamel. The ameloblasts are found close to the cusps of teeth. The ameloblasts will start producing organic (proteins) and inorganic (hydroxyapatite) materials and move toward the outer enamel epithelial layer [14].

Dentinogenesis

There are 4 phases in dentin formation:

Odontoblast differentiation: The OBs precursors are called pre- odontoblasts. When pre-obs receive the right signals from the surroundings they start growing longer, their nucleus moves to the basal side of the cell, away from the enamel layer. The cell gets an appearance of a typical secretory cell. OBs grow processes which point towards the basal lamina [14].

Matrix secretion: Dentin matrix is made mainly of collagen type I, phosphoproteins (DPP- dentinphosphoprotein; DSP- dentin sialoprotein), proteoglycans, and glycoproteins. The cells producing it are mature OBs [14].

Predentine (immature dentin) is formed by deposition of collagen type I by OBs while the cell is moving away from the basal lamina and towards the dental papilla.

Dentine mineralization: Conducted by proteins which are seen only in dentin, and no other tissue in the human body [14]

Root dentin formation: Root dentin is secreted by OB differentiated from Hertwig`s root epithelium (HRE). The collagen fibers are laid down parallel to the cement-dentine junction [14].

Adverse effects of anticancer treatment on tooth development

Anticancer treatment of children is known to cause oral complications. Mineralization of permanent teeth is a process which starts soon after birth and takes around 15 years if not counting the wisdom teeth.

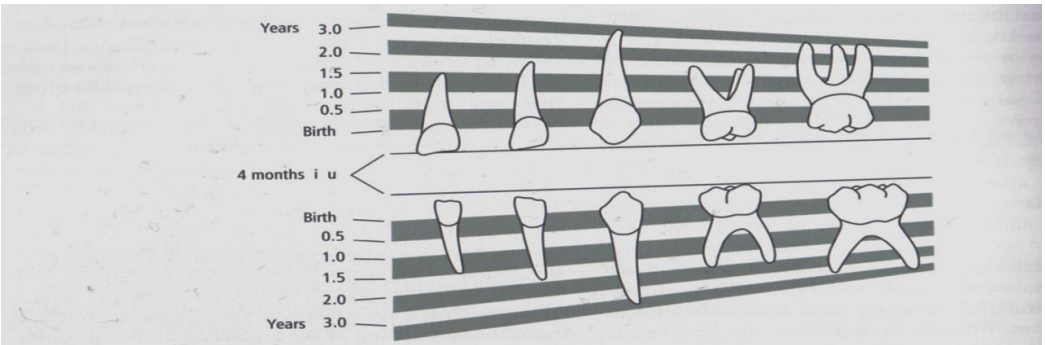


Figure 14-3 The chronology of mineralization of primary teeth.

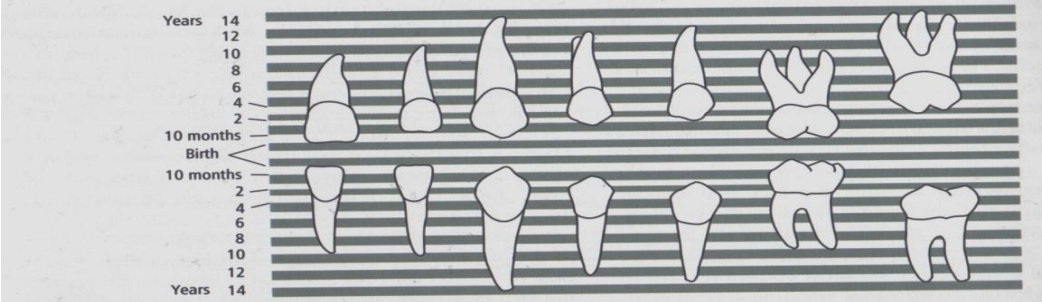
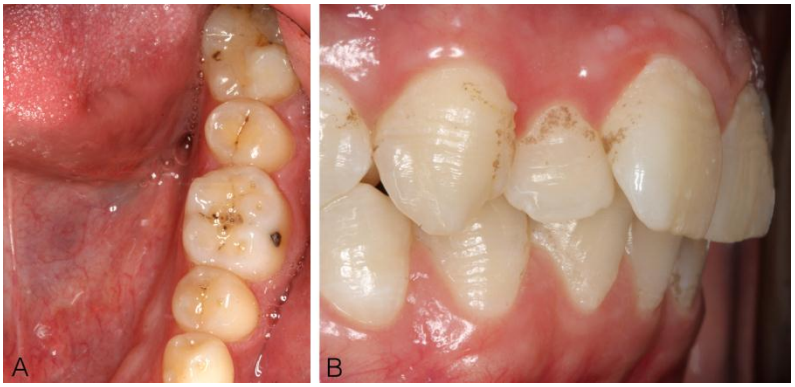


Figure 14-4 The chronology of mineralization of permanent teeth.

Table which shows chronology and mineralization of primary and permanent teeth. [15].

Root formation starts after crown formation is ended. First molars and incisors in the upper jaw are the first to start root formation. Second molars are last with root formation starting around the age of 7, 5. Trauma in generel can disturb this process. Since root formation is a slow process, changes on panoramic radiographs can be detected from one to two years after the actual trauma. Unlike other mineralized tissues in the body, teeth cannot remodel and disturbances in their structure are therefore permanent [12].

Depending on the dental age and what kind of treatment the patient has received, the effect on different teeth can vary. The same treatment can cause microdontia and/or agenesis in young age, and disturbed root formation later in life. The full impact of anticancer treatment on tooth formation is therefore not fully seen before root formation is ended. This usually happens a few years after the end of treatment [12].



Dental growth disturbances in two long-term survivors treated with cytotoxic drugs for acute lymphatic leukemia and is included in an ongoing multidisciplinary PhD-study on long term adverse effects of cancer treatment during childhood and adolescence (Wilberg P, Herlofson BB). A) Microdontia of tooth 37 (also 47) in a 30 year old man treated at the age of 2-3. B) Mineralization disturbances on several teeth in an 18 year old man treated from 2,5 years of age and in three periods [16].

Important factors affecting root formation, are type of drug, dosage and if radiation has been given. Anticancer drugs have lethal effect on tooth forming cells [12]. High doses of a chemotherapeutic drug can give necrosis, whereas smaller doses can induce cells to undergo apoptosis [17].

Signal exchange between ectomesenchyme and dentine epithelium is essential for early tooth formation. Everything that can disturb this process, cause cell death or metabolic disturbances in one or both layers, can affect tooth formation as well [12]. Anticancer treatment can affect root formation either directly or indirectly. Death of the root forming cells is a direct effect of the treatment. Disturbance in signalization between both layers is an indirect effect [15]. The effect of anticancer treatment is more detrimental when total body irradiation (TBI) is used combined with high dose chemotherapy (HDC) than when HDC is used alone [12].

HDC alone can affect tooth formation. Höllta and co-workers [12] found indications of this, but concluded that they could not reliably estimate HDC's influence on root formation completely due to the study being conducted before complete root formation in several of the study subjects [12].

The most detrimental effects of anticancer treatment, with no respect to TBI being used or not, are seen in children at age 3, 1-5 years. Fast deviding cells are most affected. At this age crown formation is over and root formation has started. The cells of HRE are the fastest deviding cells in teeth at this time. If anticancer treatment is finished before the age of three, HRE cells have not differentiated and would therefore be more resistant to the drugs. The negative effect of the treatment would be weaker as well if the treatment starts after the age of five since root formation would have started. Most teeth affected in this scenario would be second premolars and second molars since their root mineralization starts later [12].

Chemotherapeutic agents are also known to cause nerve damage to sensory or motor nerves [18]. Dental pain during anticancer treatment can be the result of drug induced neurotoxicity [19]. Radiation therapy to the head and neck region is known to cause xerostomia, radiation induced caries, and taste alterations to patients with Hodgkin`s disease [20].

Summary

Malignant lymphomas are among the most common types of cancer in children and adolecents. Recent advances in the treatment of these malignancies in children have resulted in more long term survivors (LTSs) of these types of cancer. This has also resulted in many LTSs experiencing late adverse effects due to the disease and/or its treatment that was previously unknown, among others; adverse effects influencing oral health.

The LTSs can expect to live long, and some of the adverse effects in the oral cavity can pose a significant challenge to the survivors and oral health professionals in the future. More research is needed to determine the incidence and prevalence of adverse effects in the oral cavity in cancer and cancer treatment and the possible economic impact they can pose for the LTSs and the government.

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