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Oral adverse effects during and after treatment in patients and survivors of cancers outside the head and neck region

A descriptive clinical study

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To Maren

Without your support, this would not have been possible!

CONTENTS

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals. In addition, some unpublished results are presented.

I Wilberg P, Hjermstad MJ, Ottesen S, Herlofson BB. Chemotherapy-associated oral sequelae in patients with cancers outside the head and neck region. J Pain Symptom Manage 2014; 48(6): 1060-1069. DOI 10.1016/j.jpainsymman.2014.02.009

II Wilberg P, Hjermstad MJ, Ottesen S, Herlofson BB. Oral health is an important issue in end-of-life cancer care. Support Care Cancer 2012; 20(12): 3115–3122. DOI 10.1007/s00520-012-1441-8

III Wilberg P, Kanellopoulos A, Ruud E, Hjermstad MJ, Fosså SD, Herlofson BB. Dental abnormalities after chemotherapy in long-term survivors of childhood acute lymphoblastic leukemia; 7-40 years after diagnosis. Support Care Cancer 2016; 24(4), 1497-1506. DOI 10.1007/s00520-015-2940-1

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ABBREVIATIONS

ALL	Acute Lymphoblastic Leukemia
DeI	Hölttä's Defect Index (original)
DMFT	Decayed, Missing or Filled Teeth
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core module
EORTC QLQ-H&N35	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Head and Neck module
EORTC QLQ-OH15	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Oral Health module
ESAS	Edmonton Symptom Assessment System
FEC	Fluorouracil, Epirubicin, and Cyclophosphamide (chemotherapeutic regimen)
GI	Gastro-intestinal
HSCT	Hematopoietic Stem Cell Transplantation
IASP	The International Association for the Study of Pain
ICD-10	10th revision of the International Classification of Diseases
IDeI	Hölttä's Individual Defect Index (revised)
KPS	Karnofsky Performance Status
MASCC / ISOO	Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology
MPS	Mucosal-Plaque Score
MSAS	Memorial Symptom Assessment Scale
NOPHO	Nordic Society of Pediatric Hematology and Oncology
NSAID	Non-Steroid Anti-Inflammatory Drug
OHIP-14	Oral Health Impact Profile-14
OUH	Oslo University Hospital
PC	Palliative Care
QoL	Quality of Life
RC	Root-Crown ratio
SD	Standard Deviation
SF-36	Short Form 36 health survey
TBI	Total Body Irradiation
WHO	The World Health Organization
z	An expression of how much a patient's root-crown ratio (RC_{pat}) deviates from a normal population's mean value (RC_{mean}), expressed as units of the normal population's standard deviation (SD). Calculated by the formula: $z = \frac{RC_{pat} - RC_{mean}}{SD}$

SUMMARY

Better cancer treatment has led to an increasing number of cancer survivors in Norway, but cancer is still the second most common cause of death. New treatment regimens and increased survival often imply longer treatment time and more cycles of chemotherapy. In many cases, this leads to increased risk of both short and long-term adverse effects.

The primary aim of this thesis was to investigate oral adverse effects in Norwegian cancer patients treated with chemotherapy for cancers outside the head and neck region at different phases of the disease trajectory. It also aimed to investigate if patients had received any information about oral complications or care, and if long-term survivors of childhood cancer experienced higher annual expenses for dental treatment compared to references.

Three study populations with current or previous cancer diagnoses were investigated: outpatients receiving chemotherapy, inpatients receiving palliative care, and adult survivors of childhood acute lymphoblastic leukemia. All three studies had a cross-sectional design and included an oral examination with registration of clinical findings such as caries, gingival health, mucosal disease/alterations, and dental developmental disturbances as well as oral symptoms. In the studies of the outpatients and palliative care patients, a self-report registration form including items regarding information received, a symptom assessment tool, and an evaluation tool for the patient's general condition was used. The survivors filled out a mailed questionnaire that included various questions relating to oral health and oral health expenses, which enabled a comparison of self-reported oral health and oral health expenses to a matched reference population.

Oral discomfort was highly prevalent in the outpatients receiving chemotherapy and the palliative care patients. Xerostomia, mucositis and a high number of systemic drugs were associated with oral discomfort in patients receiving chemotherapy. Xerostomia and taste alterations were associated with oral discomfort in the palliative care patients. Few patients in both groups remembered receiving information about oral complications or care. In the survivors, dental developmental defects such as microdontia, arrested root development, and enamel hypoplasia were prevalent. Receiving a cancer diagnosis at the age of five years or less and high cumulative doses of anthracyclines were associated with increased severity of dental developmental defects. Diagnosis at a higher age was associated with higher caries experience. No significant difference was found when comparing survivors to a reference population regarding annual expenses for dental treatment.

The results from this thesis indicate that there is a need for a continuous focus on how to inform about, prevent, diagnose, and manage oral cancer-related adverse effects at all stages of the disease trajectory. A systematic collaboration with dental professionals may increase the detection of oral adverse effects at an early stage; facilitate prevention and/or early treatment of oral adverse effects, thereby improving symptom management.

INTRODUCTION

The World Health Organization (WHO) describes cancer as *"a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumors and neoplasms. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs, the latter process is referred to as metastasizing. Metastases are the major cause of death from cancer"* (1).

According to the Norwegian Cancer Registry 31,651 persons were diagnosed with cancer in Norway in 2014 (2). Close to 11,000 people died of cancer that year, and 242,398 were alive after having received at least one cancer diagnosis (2). This means that many patients and survivors experience adverse effects of the disease and/or from its treatment. Further, the life expectancy in Norway is increasing, with elderly constituting a larger proportion of the population (3). The Norwegian Institute of Public Health expects a further increase of persons living with multiple chronic diseases and with an increased number of drugs used to manage these (3). Thus, both from an economical and medical point of view, the society at large and the health care services in particular have to meet this considerable challenge.

Cancer treatment is most often based on surgical interventions, radiotherapy, chemotherapy (including targeted therapy), or a combination of these. Further, adequate symptom management is an inherent part of follow-up and palliative care (PC), with symptom assessment and patient self-reported health as central issues (4). Poor symptom assessment by medical care personnel and patient misconceptions are important barriers for adequate symptom management (5-7). Oral discomfort and pain may significantly impact important aspects of everyday life (8). Inability to chew, swallow, speak and smile may interfere with sufficient nutritional intake and prevent social interaction and communication (4). In oncology in general and even more so in PC, numerous concomitant drugs are used to relieve symptoms (e.g. pain, nausea and vomiting, constipation, anxiety, depression, cachexia, and others) and to treat co-morbid conditions. Many of these drugs have adverse effects that may lead to hyposalivation (reduced salivary flow), xerostomia (subjective feeling of dry mouth), infections (e.g. fungal), taste changes, caries, soreness of oral mucosa, and nutritional deficits (6, 9-12).

There is little evidence evaluating the association between chemotherapy and dental aberrations in long-term survivors of cancer. Acute lymphoblastic leukemia (ALL) is one of the most common cancer diagnoses during childhood and adolescence. ALL is often treated with chemotherapy alone and has a high five-year as well as overall survival rate. Hence, it is an important group in which to study long-term adverse effects associated with such treatment. If long-term survivors of ALL during childhood and adolescence experience dental aberrations as late effects of cancer treatment, this might generate an increased economic

burden for oral care for the individual and/or for the society. Hence, it could influence government policy regarding funding of follow up or prophylactic care.

Most research related to oral health problems in cancer patients has been performed in patients with head and neck cancers or in patients who have received radiation therapy to the head and neck area, most likely due to the severity of the oral problems these patients experience. However, in order to improve follow-up, information and management of oral health problems for patients diagnosed with cancers outside the head and neck area, it is of great interest to explore oral short- and long-term adverse effects of chemotherapy and other medications used at different stages of the disease trajectory.

Incidence, prevalence, survival, and mortality of cancer in Norway

According to Statistics Norway, almost 5,200,000 people lived in Norway in 2014, with approximately 930,000 children being 14 years or younger (13, 14).

Incidence

Incidence: The Norwegian Cancer Registry defines incidence as *"the number of new cases (of disease) in a defined population within a specific period of time"* (2).

Almost 32,000 persons were diagnosed with cancer in Norway in 2014 (2). Persons over the age of 14 constitute 99.5% of all new cases of cancer registered from 2010 to 2014 (2). Fifty-four percent of the new cases were registered in men, with the most common diagnoses being (in descending order) prostate, lung, and colon cancers. Among women the most common diagnoses were (in descending order) breast, colon, and lung cancers (Table 1) (2). There has been an increase in the incidence of cancer for both men (3%) and women (4%) from the period 2005-2009 to 2010-2014 (2). Cancer is rare in Norwegian children below the age of 14, with only 1281 new cases registered from 2005 to 2014 (15). The most common diagnoses for both male and female children are cancer in the central nervous system and leukemias (15).

Prevalence and survival

Prevalence: The Norwegian Cancer Registry defines prevalence as *"the number or proportion of a population that has the disease at a given point in time"* (2).

Survival after cancer is the probability of continuation of life after the diagnosis (15). It is most often reported as the percentage of patients still alive after a set time (e.g. five years). However, more often The Norwegian Cancer Registry uses the term relative survival when describing survival after a cancer diagnosis. Relative survival is defined as *"the observed survival after a given period of time in a patient group, divided by the expected survival of a comparable group in the general population with respect to key factors affecting survival*

such as age, sex and calendar year of observation" (2). Relative survival is also reported as the percentage of patients alive after a given time period (i.e. five years).

Survival after receiving a cancer diagnosis is steadily increasing for both adult and childhood cancers, and in 2014 there were more than 240,000 cancer survivors living in Norway, which is an increase of almost 77,000 survivors since 2004 (2, 15). The improvement of prognosis is attributed to early diagnosis due to national screening programs and increased attention to cancer in the population and health care services, as well as increased duration, intensity and quality of the treatment (2).

Mortality

Mortality: The WHO defines mortality data as the *"number of deaths by place, time and cause"* (16).

Approximately 11,000 died of cancer in Norway in 2014, with lung and gastrointestinal cancer among the most common causes of cancer deaths in both sexes (Table 1) (2). Further, breast and prostate cancer are among the most common causes of cancer deaths in females and males respectively (2).

Table 1: Incidence, prevalence, survival, and mortality data from 2014 for the most prevalent diagnoses included in this thesis.

Diagnosis	Incidence	Prevalence	Five-year relative survival [A]	Mortality
Breast cancer	3,324	42,786	88%	669
GI cancer [B]	6,462	36,106	~6% - ~66% [D]	3,221
Lung cancer	3,019	6,619	13% [E] - 19% [F]	2,158
Prostate cancer	4,889	41,841	91%	1,093
ALL[C]	32	- [G]	88% [H]	- [G]

Two recent reports from The Cancer Registry of Norway were used in the compilation of this table (2, 15). [A] Patients evaluated between 2012 and 2014. [B] GI cancer: Gastro-intestinal cancer refers to malignant diagnoses of the alimentary tract (including the esophagus, stomach, small intestine, large intestine, rectum, and anus) and accessory organs of digestion (i.e. liver, biliary system, and pancreas); but excluding the mouth and pharynx (2). [C] ALL: Acute Lymphoblastic Leukemia in children and adolescents (14 years and younger). [D] Lower number is pancreatic cancer; higher number is cancer of the rectum and rectosigmoid. [E] Males [F] Females [G] Not reported. [H] Patients treated between 2000 and 2009.

Main treatment principles of cancer

Surgery, radiation therapy, chemotherapy (including targeted therapy), or combinations of these constitute the basis of cancer treatment. Further, detection, prevention, and adequate treatment of symptoms of disease and adverse effects are important during treatment and follow-up, and cornerstones of PC. As this thesis focuses on the short- and long-term oral adverse effects of anti-neoplastic and other medical treatment, surgical interventions and radiation therapy will not be discussed in detail.

Surgical interventions

Surgery is important in the treatment of most solid tumors, mainly through resection of primary tumors and metastases (17, 18). Often chemotherapy and/or radiation therapy will be used to reduce tumor size prior to surgery and facilitate resection of the tumor (17, 18). Surgery is essential to diagnosing and staging of the disease through biopsies (19). Surgery also plays an important role in PC (e.g. stenting because of tumor obstruction of the gastrointestinal tract) and reconstruction (e.g. breast) after treatment of the primary cancer (20, 21).

Radiation therapy

Similar to surgery, radiation therapy is an integral part of cancer therapy. Radiation therapy uses ionizing radiation to induce apoptosis (programmed cell death) in target cells due to DNA damage. Rapidly proliferating cells (e.g. many malignant cells, but also proliferating normal cells) are more susceptible to radiation therapy than differentiated, non-proliferating cells. Radiation therapy can be applied with curative intent (e.g. localized prostate cancers) (22). However, more often it is applied as adjuvant (therapy given in addition to the primary therapy to obtain better results; e.g. after surgery in breast cancer) or neoadjuvant (therapy given prior to the main therapy; e.g. to reduce size of a tumor before surgery) therapy (19, 23, 24). Radiation therapy is also used with palliative intent e.g. to alleviate pain from bone metastases (20, 25, 26).

Chemotherapy

Conventional chemotherapy are broadly cytotoxic to proliferating cells (27). Susceptible neoplastic tissue with high proliferation rate is easily influenced by chemotherapy through various mechanisms of action (Table 2). However, this is also the case with healthy cells with high turnover, for example epithelial cells in the oral mucosa, and cells involved in the development of teeth, resulting in short- and long-term adverse effects to the oral mucosa (e.g. mucositis and candidiasis), salivary glands (e.g. hyposalivation and xerostomia), and teeth (e.g. caries and developmental aberrations) (28-56). Hence, the increasing success of cancer therapies comes at a cost to the patients. Sometimes oral adverse effects can be dose limiting and consequently compromise prognosis (9, 38, 57-59). Further, severe pain and long standing nutritional problems can contribute to a reduced Quality of Life (QoL) and may also have a negative social impact often for the rest of the patients' lives (9, 38, 57-60).

Novel anti-cancer drugs that target the molecular drivers of tumor development are collectively called targeted therapeutics and can be used to facilitate personalized therapy (19, 61-64). These drugs have a wide variety of mechanisms of action directed at specific cancer-associated signaling pathways, and only patients with tumor cells expressing the specific target will benefit from such therapy (27). The effects of such drugs can be as varied as blocking tumor angiogenesis (e.g. bevacizumab) (65), inhibit cell growth and induce apoptosis (e.g. cetuximab) (62, 65), activate the immune system leading to cell death (e.g. rituximab) (66), or having hormone or hormone antagonistic properties that inhibit growth of tumors (e.g. tamoxifen) (Table 2) (67).

Palliative care

The WHO defines PC as *"an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual"* (68). The new WHO definition of PC affirms that the principles of PC are applicable at all stages during the disease trajectory. However, many patients are not referred to PC specialist care until very late in the trajectory.

The term advanced cancer is often used to describe patients where the cancer has metastasized and usually cannot be cured or controlled by treatment. Almost all advanced cancer patients need PC for optimal symptom management during the last months of life (20, 69). In Norway, cancer patients constitute over 95% of the patients treated in PC units and they are also the largest patient population among patients with PC needs in primary health care (20). PC is not a medical specialty in Norway, but physicians from many different medical specialties have PC as their primary occupation. PC is multidisciplinary and may include other professions as integral parts of the team according to the patient's need (e.g. nurses, physiotherapists, social workers, clinical nutritionists, religious workers, psychologists, and others) (20). Oral health care personnel have so far not been involved in PC in Norway.

The goal of PC is to maintain the best quality of life and optimal symptom management until death through a multidisciplinary approach (20). Hence there is a multitude of different care and treatment principles in PC spanning from spiritual guidance, via economic planning to complex medical treatment (20). To describe all these care principles is outside of the scope of this thesis, but pharmacological treatment is an important part of symptom management. Hence, a brief overview of the most commonly utilized drug classes employed in symptom management in PC is presented below, as these can severely influence oral health (Table 3).

Table 2. Conventional chemotherapeutic drugs, targeted therapy drugs, and hormones used in the study populations (I-III): classification, drug, mechanism of action, registered oral adverse effects, and main indications in cancer therapy*

Drug (e.g. brand name)	Mechanism of action	Oral adverse effects	Main indications	Study
Alkylating agents				
Cyclophosphamide (Sendoxan)	DNA-DNA crosslinks resulting in cell death	M, T, Par, A↓	Lymphoma, leukemia, myeloma, and palliative care in metastatic cancers	I, II, III
Trofosfamide (Ixoten)	DNA-DNA crosslinks resulting in cell death	M, A↓	Lymphoma (palliative)	II
Temozolomide (Temodal)	Alkylate DNA resulting in cell death	M, T, FI, VI, C	Glioma and skin cancer	II
Dacarbazine (Dacarbazine)	Alkylate DNA resulting in cell death	Par, A↓	Hodgkin's lymphoma, sarcoma, and malignant melanoma	I
Procarbazine (Natulan)	DNA Breakage	M, X, VI, A↓	Lymphoma, and glioblastoma	I
Carmustine (Gliadel)	Alkylate DNA resulting in cell death	M	Brain and lung cancer. Lymphoma, leukemia, and melanoma	III
Streptozotocin (Zanosar)	Alkylate DNA resulting in cell death	M, A↓	Pancreas cancer	I
Antimetabolites				
Fluorouracil (Flurablastin)	Block DNA replication by inhibiting thymidylate synthase	M, A↓	Breast and GI cancer	I, II
Capecitabine (Xeloda)	(Fluorouracil pro-drug) Block DNA replication by inhibiting thymidylate synthase	M, X, T, P, Par, FI, VI, A↓	GI and breast cancer	I
Fludarabine (Fludara)	Inhibits DNA synthesis and repair by interfering with ribonucleotide reductase and DNA polymerase	M, VI, A↓	Leukemia	I
Cytarabine (Cytarabine)	Block DNA replication by replacing cytidine during synthesis	M, A↓	Leukemia	III
Gemcitabine (Gemzar)	Block DNA replication by replacing cytidine during synthesis	M, A↓	Bladder, pancreatic, lung, ovarian, and breast cancer	I, II
Methotrexate (Methotrexate)	Block DNA synthesis by inhibiting dihydrofolate reductase	M, T, Par, FI, VI, G, A↓	Leukemia, lymphoma, and sarcoma. Breast, H & N, trophoblastic, and bladder cancer	I, II, III
6-Thioguanine (Lanvis)	Block DNA replication by replacing guanine during synthesis	M	Leukemia	III
6-Mercaptopurine (Xaluprine)	(6-Thioguanine pro-drug) Block DNA replication by replacing guanine during synthesis	M, A↓	Leukemia	III
Tubulin inhibitors (Plant alkaloids)				
Vincristine (Oncovin)	Inhibit mitosis by interfering with microtubulin	M, P, A↓	Acute leukemia, Hodgkin's lymphoma, lymphosarcoma, reticulum cell carcinoma, rhabdomyosarcoma, neuroblastoma, and Wilms' tumor	I, II, III
Vinorelbine (Navelbine)	Inhibit mitosis through interaction with tubulin	M, T, P, FI, VI, A↓	Breast and lung cancer	I, II
Vinblastine (Velbe)	Inhibit mitosis by interfering with microtubulin	M, P, A↓	Palliative treatment	I
Paclitaxel (Taxol)	Inhibit breakdown of microtubules, thereby induce apoptosis	M, X, T, P, Par, FI, VI, A↓	Breast, lung, ovarian, and pancreatic cancer. Kaposi's sarcoma.	I, II
Docetaxel (Taxotere)	Inhibit breakdown of microtubules, thereby induce apoptosis	M, X, T, P, Par, FI, A↓	Breast, lung, prostate, ventricular, and head and neck cancer	I, II
Platinum-based compounds				
Carboplatin (Carboplatin)	Crosslink and shorten of DNA strands	M, T, Par, A↓	Ovarian and lung cancer	II
Cisplatin (Cisplatin)	Crosslink DNA strands	M, T, Par, A↓	Testicular, lung, and ovarian cancer	I, II
Oxaliplatin (Oxaliplatin)	Crosslink DNA strands	M, T, P, Par, A↓	GI cancer	I
Anti-cancer antibiotics				
Doxorubicin (Adriamycin, Caelyx, Myocet))	Intercalate in DNA, inhibit topoisomerase, and induce DNA breakage through free radicals	M, X, T, P, FI, VI, G, A↓	Bladder, breast and lung cancer. Lymphoma, leukemia, sarcoma, neuroblastoma, and Wilms' tumor	I, II, III

Table 2 continued

Daunorubicin (Cerubidin)	Intercalate in DNA, inhibit topoisomerase, and induce DNA breakage through free radicals	M	Leukemia	III
Epirubicin (Epirubicin)	Intercalate in DNA, inhibit topoisomerase, and induce DNA breakage through free radicals	M, P, A↓	Breast, GI, ovarian, H & N, ventricular, pancreatic, and bladder cancer. Lymphoma	I
Bleomycin (Bleomycin)	Induce DNA breakage through free radicals	M, P, A↓	Lymphoma, SCC, and testicular cancer	I
Other cytotoxic drugs				
Etoposide (Vepesid)	Breaks DNA through inhibition of topoisomerase	M, T, A↓	Acute leukemia and malignant lymphoma. Lung and testicular cancer	I, II
Irinotecan (Irinotecan)	Breaks DNA through inhibition of topoisomerase	M, A↓	GI cancer	I
Asparaginase (Asparaginase)	Deprive cancer cells of asparagine leading to cell death.	-	Leukemia, and lymphoma	III
Hydroxycarbamide (Hydrea)	Inhibit ribonucleotide reductase	M, A↓	Leukemia	III
Signal inhibitors*				
Erlotinib (Tarceva)	EGFR inhibitor, induce discontinuation of cell proliferation or cell death	M	Lung and pancreatic cancer	II
Monoclonal antibodies*				
Trastuzumab (Herceptin)	HER2 inhibitor, arrest cell proliferation and lead to an immune response and cell death	M, X, T, P, Par, VI, A↓	Breast, and ventricular cancer	I
Bevacizumab (Avastin)	Binds VEGF. Block angiogenesis.	M, T, A↓, ONJ	GI, breast, lung, kidney, ovarian, Fallopian tube, peritoneal, and cervix cancer	I
Cetuximab (Erbitux)	EGFR inhibitor, inhibit cell growth and, induce apoptosis.	M, FI, A↓	SCC and GI cancer	I
Rituximab (MabThera)	Binds to CD-20 antigen on B-cells, leading to an immune response and cell death	M, T, Par, FI, VI, A↓	Lymphoma	I
Hormones and hormone antagonists				
Bicalutamide (Casodex)	Block androgen stimulus	X, AP↓	Prostate cancer	I, II
Leuprorelin (Procren Depot, Eligard, Enanton)	GnRH analog causing an anti-androgen effect	M, X, T, Par, FI, VI, G, A↕	Prostate cancer	I, II
Goserelin (Zoladex)	GnRH analog causing an anti-androgen effect	Par	Prostate and breast cancer	I, II
Polyestradiol phosphate (Estradurin)	Human estrogen. Anti-androgen effect	-	Prostate cancer	I
Fulvestrant** (Faslodex)	Estrogen receptor antagonist	A↓	Breast cancer	I
Letrozole** (Femar)	Non-steroidal aromatase inhibitor, inhibit estrogen synthesis	M, X, T, Par, A↕	Breast cancer	I, II
Megestrol (Megace)	Progestin. Mechanisms of action not clear, but anti-estrogen effect appear to be important.	A↑	Breast cancer	I, II
Tamoxifen** (Nolvadex)	Anti-estrogen effect in breast tissue	T, Par	Breast and endometrial cancer	I, II
Anastrozol** (Arimidex)	Non-steroidal aromatase inhibitor, inhibit estrogen synthesis	T, A↓	Breast cancer	I
Exemestane** (Aromasin)	Steroidal aromatase inhibitor, inhibit estrogen synthesis	A↓	Breast cancer	I
Cytokines				
Filgrastim (Neupogen)	G-CSF analog (Immunostimulant)	M, A↓	Neutropenia due to chemotherapy or HSCT	I

* The Norwegian (70), Swedish (71), and Danish (72) pharmaceutical product compendiums, as well as Dahl et al 2009 (73) and Fleming 1997 (74) were used as references in the compilation of this table. ** Targeted therapy. **Abbreviations (Mechanism of action)**: VEGF: Vascular Endothelial Growth Factor, G-CSF: Granulocyte Colony-Stimulating Factor, EGFR: Epidermal Growth Factor Receptor, HER2: Human Epidermal growth factor Receptor 2, GnRH: Gonadotropin-Releasing Hormone. **Abbreviations (Oral adverse effects)**: M: Mucositis/stomatitis; X: Xerostomia, T: Taste changes; P: Pain; Par: Paresthesia; FI: Fungal infection; VI: Viral infection; G: Gingivitis; C: Caries; A↓↑↕: Appetite increased, reduced or both; ONJ: Osteonecrosis of the jaw. **Abbreviations (Indications)**: GI: Gastro intestinal; SCC: Squamous Cell Carcinoma, HSCT: Hematopoietic Stem Cell Transplantation

Table 3. Classes of drugs used as concomitant medications in studies I and II with registered oral adverse effects*

Drug class	Registered oral adverse effects	Study
Antidepressants	M, X, T, Par, A↕	I, II
Anxiolytics, sedatives, and anticonvulsants	M, X, T, Par, VI, A↕	I, II
Antimigraine	X, T, P	I, II
Antibiotics	M, X, T, FI	I, II
Corticosteroids and immunosuppressants	FI, VI, A↑	I, II
Diuretics	X, T, P, A↓	I, II
Beta-blockers	X, T	I, II
Other antihypertensiva	M, X, T, A↕	I, II
Antihyperlipidemic	T, A↓	I, II
Antipsychotics	X, A↓	I, II
Antihistamines	X, T, A↑	I, II
Antiemetics	M, X, T, FI, A↑	I, II
Anti-diarrheal	X	I, II
Anti-diabetic	T, A↓	I, II
Anticholinergica	M, X	I, II
Anti-parkinson	X, T	II
Acid-reducing drugs	M, X, T, FI	I, II
Opioids	M, X, T, G, A↓	I, II
Other analgesics	M, T, A↓	I, II
Bisphosphonates	M, X, T, P, A↓, ONJ	I, II
Other	C, A↓	I, II

* This table was compiled using information from the Norwegian, Swedish and Danish pharmaceutical product compendiums (70-72). **Abbreviations (Oral adverse effects)**: M: Mucositis/stomatitis; X: Xerostomia, T: Taste changes; P: Pain; Par: Paresthesia; FI: Fungal infection; VI: Viral infection; G: Gingivitis; C: Caries; A↓↑↕: Appetite increased, reduced or both; ONJ: Osteonecrosis of the jaw

Oral adverse effects of chemotherapy and symptom management

Many definitions of adverse drug effects/reactions have been proposed (75-78). Earlier definitions often exclude adverse effects that are not harmful, but only inconvenient to the patient (75, 76). In this thesis the definition proposed by Edwards and Aronson in Lancet in 2000 was used: an adverse effect is *"an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product"* (77). This definition includes adverse effects that are detected by the patient, but that might seem trivial to a physician (77, 78). Adverse effects of cancer therapy are characterized as either acute or chronic.

Acute adverse effects are experienced during drug treatment, but resolve within a short time after discontinuation of a drug. These reactions can be predictable if they are related to drug pharmacology or dose, but can also be unpredictable if the mechanism behind the reaction is unknown (77, 79). It should be noted that when targeted therapy is combined with conventional therapy, known adverse effects can be enhanced, or new and unexpected adverse effects may occur (80).

Chronic adverse effects are marked by long duration or a frequent recurrence. Often the chronic adverse effects are further divided into several sub-categories; e.g. long-term (effects that becomes apparent during therapy and persists), late (the risk of an adverse effect increases with increased exposure to drug), or delayed effects (becomes apparent after the end of drug use) (77-79), although these terms are often used interchangeably in the literature. For many novel drugs used in cancer therapy little is known of their chronic oral adverse effects (80, 81).

A short summary of the most common acute and chronic oral adverse effects of drug based cancer therapy and PC is presented in table 4 and the text below.

Table 4: The most common oral adverse effects associated with drug based cancer therapy and symptom management.

Adverse effect	Acute	Chronic	Comments
Mucositis	x		
Pain	x	x	
Xerostomia and hyposalivation	x	(x)	Often chronic if polypharmacy persists
Taste and smell alterations	x	(x)	Often chronic if polypharmacy persists
Infections			
Bacterial	x	x	
Fungal	x	(x)	Often chronic if polypharmacy persists
Viral	x		
Swallowing dysfunction	x	x	
Dental developmental defects		x	If treated while teeth are developing

Mucositis

Mucositis is a potentially serious inflammatory process, which is a frequent adverse effect of chemotherapy (Table 2) and/or radiation therapy (6, 82). Approximately 70-80% of patients treated with high-dose chemotherapeutic regimens and hematopoietic stem cell transplantation (HSCT), and approximately 40% of patients treated with standard dose chemotherapeutic regimens experience this adverse effect to some degree (83). It can afflict the mucosa of the whole alimentary tract (the oral cavity; the pharyngeal, laryngeal, and esophageal regions; and the stomach, small intestine, and large intestine) (56, 82). The clinical presentation is very painful erythema and/or ulcers in the oral cavity; and/or severe pain, nausea, vomiting and diarrhea if it is present in the rest of the alimentary tract (82, 84-86). Consequently, mucositis may e.g. impair nutritional status, lead to dose-reduction and reduce prognosis (86). Mucositis has also been registered when targeted therapies are used, but to a lesser extent than with conventional chemotherapy (80).

Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology (MASCC / ISOO) recently conducted a series of reviews to update their clinical guidelines regarding how to prevent development and provide better treatment of mucositis (86-95). However, few guidelines could be established concerning mucositis associated with chemotherapy (86-95). Basic oral care and continuous assessment of the oral cavity is recommended to prevent mucositis, reduce symptoms, and/or to prevent secondary infections associated with mucositis (82, 90, 96). For treatment regimens containing 5-FU or melphalan; cryotherapy is recommended to prevent or reduce mucositis (82, 96). Treatment options of pain related to oral mucositis are limited, but local treatment with topical application of a local analgesic (i.e. lidocaine) or a morphine rinse is common (20, 82, 89). If local treatment does not alleviate symptoms, parenteral or transdermal opioid treatment is indicated (20, 89, 96). In PC, the treatment principles remain the same. However, the severe symptoms associated with mucositis may not be as well tolerated when treatment is given with palliative intent as with curative intent, with discontinuation of the treatment as a more likely result to enhance the patient's quality of life (10).

Oral pain

The International Association for the Study of Pain (IASP) define pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (97). Further, they define neuropathy as "a disturbance of function or pathological change in a nerve" (98). Pain is common in patients receiving curative therapy and in patients with advanced cancer (99, 100). In cancer patients, the most common causes of oral pain are the cancer itself or adverse effects of treatment of cancer and related symptoms (6). Mucositis (described above), infections (described below) and neuropathic pain are examples of symptoms and adverse effects that may cause oral pain (6).

In patients with advanced cancer, pain relief is paramount, with the WHO analgesic ladder (101, 102) as the underlying principle of treatment (20, 69, 103). The analgesic ladder is

based on administering different analgesics in a three-step approach to alleviate pain and obtaining pain control at the lowest and most cost effective level. The lowest step of the ladder is non-opioids (e.g. non-steroid anti-inflammatory drugs (NSAIDs) or paracetamol ± adjuvants), the second step is mild opioids (e.g. codeine or tramadol ± non-opioids and/or adjuvants), and the last step is strong opioids (e.g. morphine ± non-opioids and/or adjuvants) (69). At all steps, adjuvant drugs such as antidepressants, glucocorticoids or anticonvulsants may be used to manage the pain (69). With the use of the analgesic ladder and the updated treatment guidelines most cancer related pain is now manageable (69). However, a recent meta-analysis showed that despite improvement, pain is still reported to be undertreated in approximately one-third of patients with cancer (104).

Neuropathic pain is a severe oral adverse effect associated with several chemotherapeutic drug classes e.g. tubulin inhibitors and platinum based drugs (Table 2) (6, 105). Neuropathic pain is difficult to treat, and treatment regimens usually involve antidepressants, anticonvulsants, systemic analgesics, and biopsychosocial therapy; with most drugs used having further oral adverse effects (Table 3) (6, 69, 105). Neuropathic pain can be an acute adverse effect of chemotherapeutic drugs, but can become chronic if the nerve damage is permanent (105).

Bisphosphonates and corticosteroids are also used in pain management (Table 3) (103). Further, palliative radiation therapy (especially targeting bone metastasis), palliative surgery (e.g. stabilizing a pathological fracture), treatment with antiresorptive drugs (e.g. bisphosphonates) to reduce the number of bone related incidents, and systemic treatment targeting the cancer cells (e.g. with hormone therapy, traditional chemotherapeutic drugs, or targeted therapy) may lead to good pain control (20).

Xerostomia and hyposalivation

Saliva is important to taste, swallowing, speech, oral clearance, maintaining the oral ecosystem, prevention of disease, healing, and much more (6, 31, 106). Hence, xerostomia and a prolonged reduction of the quantity or quality of saliva may leave a patient prone to infections (e.g. fungal and caries) and can enhance functional problems (e.g. taste, swallowing, and speech) (6, 10). Many of the chemotherapeutic, targeted and concomitant drugs, as well as drugs used to treat co-morbidities have xerostomia and/or hyposalivation as known adverse effects (Tables 2 and 3) (106). Hence, both xerostomia and hyposalivation are known adverse effects of frequently used drugs in cancer therapy and symptom management.

Jensen and co-workers in 2010 conducted a review of xerostomia and hyposalivation induced by cancer therapies on behalf of the MASCC / ISOO that resulted in two articles (31, 107). Their findings indicated that approximately 50% of patients receiving chemotherapy alone, experience xerostomia during treatment (31). However, results varied and were dependent on diagnosis, treatment regimens, and patient populations included in the studies (31). They also reported that salivary flow rates remained relatively unchanged

during chemotherapy (31). Studies regarding chronic xerostomia and hyposalivation after conventional chemotherapy provide diverging results (31). Results from some studies (conducted on patients with hematological malignancies) show no change in stimulated or unstimulated saliva flow, while others (conducted on patients with solid or hematological malignancies) report both persisting xerostomia and reduced salivary flow up to 7 years after chemotherapy (31). Xerostomia is experienced by about 80% of the PC population (10, 12). Hyposalivation has not been investigated to the same degree as xerostomia, probably due to the time needed to assess this adverse effect. However, with the multitude of drugs with xerostomia as a known adverse effect used in PC, it is likely that a large proportion of these patients also suffer from hyposalivation (Table 3). Further, PC patients are frequently dehydrated which may exacerbate the problem further (10, 20).

Management strategies vary according to the individual patient, but are mainly symptomatic (6, 107, 108). The main principles of treatment for xerostomia and hyposalivation are stimulation of residual secretory capacity in the salivary glands, or lubricating/moisturizing the oral cavity. None of the guidelines set forth by MASCC / ISOO concern problems arising from chemotherapy, only radiation therapy (107). Although there is little evidence for any specific intervention, many of the treatment strategies reviewed are used clinically to give short-term relief of xerostomia / hyposalivation in patients receiving chemotherapy and symptom management (6, 106-109). Such management strategies include: 1) reduction/elimination of dehydration through an increased intake of water and an avoidance of caffeine, 2) the use of lubricating / moisturizing agents and salivary substitutes, 3) to avoid use of tobacco and alcohol, 4) measures to reduce mouth breathing, and 5) gustatory and masticatory stimulation with lozenges, chewing-gum, or candy (6). Patients are also recommended to avoid sugar and snacks in their diet to reduce the risk of caries, and some patients will gain some symptom relief from avoiding spicy or acidic food/beverages (6, 106, 108, 109). Further, drugs that increase salivary secretion, (i.e. pilocarpine, cevimeline, and bethanechol) may be beneficial to some patients with chronic hyposalivation (6, 108).

Altered perception of taste and smell

Alteration in taste (dysgeusia) and/or smell (dysosmia) are common adverse effects of many drugs used in antineoplastic treatment regimens, but also of many other commonly used drugs (Tables 2 and 3) (6, 12, 39, 110-113). Both taste and smell are further linked to the patient's ability to perceive flavor in food and drink (110). Hence, dysgeusia and dysosmia can lead to malnutrition, weight loss, and reduced quality of life in cancer patients (110, 113). The etiology of these alterations is not completely known. However, nerve damage, interference with receptor activity, reduced saliva production, secretion of drug into the oral cavity, and others are suggested as possible mechanisms of action of how chemotherapeutic drugs can cause taste and smell alterations (6, 110, 111). Further, concomitant drugs, psychological effects, infections, and/or poor oral hygiene play a crucial role in the development of taste alterations (6, 110). Both taste and smell alterations are reported to resolve within a short time after conclusion of chemotherapy (110, 111). In PC, dysgeusia is

more likely to persist as many drugs that can cause e.g. hyposalivation are used in symptom management. Saliva is an essential component to taste perception through its role as a carrier of tastants to the taste buds (6). In a MASCC / ISOO review, Hovan and co-workers found no evidence of effective treatment or prevention strategies for dysgeusia and dysosmia in patients receiving chemotherapy (110). However, many measures are used in clinical practice to try to reduce the problems associated with these adverse effects (e.g. remove causative drug if possible, oral hygiene measures, infection control, increasing flavor of food using tastants, using candy / chewing gum to mask unpleasant taste, zinc-supplement, or different drugs) (6, 110).

Oral infection

Cancer patients have a high risk of infection (fungal, bacterial, and/or viral) due to cancer therapy, immunosuppression, poor nutritional status, and concomitant medications and diseases (20, 114-116). The oral cavity is especially vulnerable to opportunistic infections during cancer treatment due to a decreased barrier function (e.g. as a result of mucositis, atrophy of the mucosa, and teeth and periodontium that inserts through the mucosal barrier), the loss of protectoral properties of saliva, and/or the amount and diversity of both commensal and introduced microbes and viruses in the oral cavity (32, 106, 109, 114, 117-120). Infection can lead to oral discomfort, compromise nutrition, prolong hospital stays, dose reduction or change in chemotherapeutic regimen, and be life threatening if proper treatment is not implemented (20, 117, 119, 121).

Thus, the prevention of oral infections is important during all cancer therapies to prevent minor infections from developing into systemic and potentially life-threatening infections (122). Many cancer centers have implemented oral care protocols to prevent infections of dental and periodontal origin, although most concern patients scheduled for radiotherapy or high-dose chemotherapy with HSCT (122).

Fungal infections

Almost 40% of patients receiving chemotherapy and 8-94% of the PC population experience an oral fungal infection, with different candida-species as the most common pathogens (32, 121, 123-125). Some fungi, especially *candida albicans*, are a part of the commensal microbiota of the oral cavity and cause few infections in healthy individuals (32). However, in the immunocompromised cancer patient with hyposalivation, local tissue damage, and altered oral microbiota they often act as opportunistic pathogens and may cause local and systemic disease (32). *Candida albicans* is the most common pathogen in fungal infections. However, other candida (most notably: *c. tropicalis*, *c. dubliniensis*, *c. krusei*, and *c. glabrata*) and aspergillus species are known to cause such infections with resistance to antifungal drugs (azoles) as a consequence (6, 123, 124, 126). Invasive fungal infections have a high mortality rate (32). Due to the high prevalence and serious implications of fungal infections in cancer patients, prophylactic anti-fungal treatment with a systemic azole or amphotericin B are often used (6, 20, 32, 117, 127). Fluconazole reduces fungal infections in cancer

patients and is the most commonly used drug, with the other drugs reserved for refractory disease (6, 20, 32, 127). However, Cochrane reviews recommend the use of amphotericin B administered intravenously as the preferred drug to prevent or treat disseminated fungal infection in immunocompromised patients, as it is the only drug associated with reduced mortality (127, 128). Nystatin is not recommended as an antifungal drug in immunocompromised patients (129). Further, local application of miconazole or clotrimazole cream are used to treat rhagades and denture-related stomatitis (20).

Bacterial infections

A heightened risk of infection and reduced mucosal barrier function make patients receiving chemotherapy and frail patients more susceptible to opportunistic bacterial infections, both local (e.g. periodontitis and salivary gland infections) and systemic (20, 115, 121, 122, 130). The oral cavity is mentioned as a possible site of origin of infection in many studies regarding systemic bacterial infections in patients with neutropenia (114, 119, 121, 123, 130, 131). If needed, antibiotic treatment should be based on results from culture (132).

Caries

Caries in cancer patients is linked to changes in saliva composition and flow (6). Hence, prevention of caries should include optimization of oral hygiene and management of xerostomia and hyposalivation (6). Caries may lead to infection of the dental pulp and apical periodontitis. Little is known about caries in PC populations, but it may be induced that PC patients are at a high risk of developing caries due to their polypharmacy, high rates of xerostomia, and reduced general condition. In a MASCC / ISOO review of dental disease in cancer patients, Hong and co-workers reported that caries is more prevalent (37%) after chemotherapy than after other cancer treatment modalities such as radiotherapy (24%) or chemoradiotherapy (21%) (122). However, caries experience, reported as the number of decayed, missing or filled teeth (DMFT), following chemotherapy are reported to be much lower (DMFT 4.5) than after radiotherapy (DMFT 17.0) (122). However, it should be noted that all of the studies concerning chemotherapy were conducted in survivors of hematological malignancies during childhood and adolescence, while the studies concerning radiotherapy were conducted in adult survivors of head and neck malignancies (122). Caries experience is also reported to be higher in survivors who have received chemotherapy only compared with healthy reference populations (122). Further, dental infections and abscesses have been shown to occur in approximately 6% of patients receiving chemotherapy (122). There is concern that infection spreading through the periapical tissues may cause life-threatening events in immunocompromised patients (122). Hence, prevention and management of caries and apical disease, including extractions if necessary, is important both prior to and during chemotherapy (122, 131). However, oral health protocols are more commonly used for patients undergoing radiotherapy or chemoradiotherapy, than for patients undergoing chemotherapy (122). This may result in patients entering chemotherapy with untreated lesions and lack of adequate prophylactic measures and interventions during and after therapy (122, 133).

Gingivitis/Periodontitis

Gingivitis is inflammation of the gingiva, most often caused by bacterial plaque at the gingival margin. This implies a breakdown of the mucosal barrier function and a potential site of entry for bacteria and other pathogens. Gingivitis is a common finding in patients receiving chemotherapy, and good oral hygiene, supplemented by chlorhexidine rinse when needed, is recommended to manage it (122). Periodontitis is inflammation of the supporting structures of teeth leading to progressive bone loss. Periodontitis is of special concern regarding spread of oral pathogens as it is known to cause bacteremias and is linked to several systemic diseases (134, 135). Flare up of chronic periodontal infections during cancer therapy is well known, and elimination of periodontal disease is recommended prior to treatment start as well as a maintenance regimen during therapy (131, 134).

Sialadenitis

Bacterial acute sialadenitis is an infection of the salivary glands often ascribed to retrograde infection of the glands by commensal bacteria due to reduced or blocked flow of saliva (108, 136, 137). Hence, chemotherapy and concomitant drugs that cause reduced salivary flow predispose for this infection (118).

Viral infections

Viral infections in the oral cavity during cancer treatment are a source of discomfort and pain to the patient (138). Further, it is associated with decreased fluid intake and compromised nutritional status that can lead to hospitalization (138). Between 0% (radiotherapy to the head and neck) and 80% (patients receiving HSCT) of cancer patients experience primary or reactivation of latent viral infections during treatment, particularly herpes simplex infections (115, 138). In neutropenic patients, the prevalence is close to 50%, and is higher among those with oral ulcers (138). In PC, Herpes simplex, type 1, is the most common viral infection (20). Prior to the development of effective drugs, viral infections were associated with death in patients undergoing HSCT (138). The anti-viral drugs acyclovir and valaciclovir are successfully used to prevent viral infections in cancer patients, but Elad and co-workers found no studies evaluating treatment protocols for active infections in a review performed for MASCC / ISOO (138).

Swallowing dysfunction

Problems swallowing (dysphagia) is a serious adverse effect of cancer and cancer therapies that can be fatal (36). Further, it may impair the QoL, social function and nutritional status of cancer patients (36). Swallowing is a complex process involving both voluntary and reflexive elements. Many of these processes can be influenced during cancer therapy (36). Further, the patient's subjective feeling of dysphagia can be exacerbated by the presence of xerostomia (36). Management of dysphagia is many faceted, adapted to the individual patient's needs, and requires a multidisciplinary approach (36).

Dental developmental defects

Developmental defects affecting the teeth are common long-term adverse effects of cancer treatment in childhood and adolescence, but most studies concern survivors who have received radiotherapy and/or HSCT (139). These treatments induce more severe developmental defects than chemotherapy (139). However, there is evidence of an association between chemotherapy and dental developmental defects such as enamel hypomineralization, enamel hypoplasia, delayed or arrested tooth development, microdontia, and hypodontia (139). Further, dental defects are more prevalent in survivors who received chemotherapy before the age of five compared to those who were older when treated, corresponding to when the teeth are under development (139). Drug classes such as alkylating agents (e.g. cyclophosphamide) and tubulin inhibitors (e.g. vincristine) have been associated with dental developmental defects in humans (139), whereas animal models have indicated that anti-cancer antibiotics / anthracyclines (e.g. doxorubicine) may cause aberrations to developing teeth (140).

AIMS OF THE THESIS

The overall aim was to investigate the subjective and objective oral adverse effects in cancer patients treated with chemotherapy for cancers outside the head and neck region at different phases of the disease trajectory.

The specific aims were:

Paper I:

- To assess and examine oral health and adverse effects during chemotherapy in patients treated for cancers outside the head and neck region.
- To investigate if the patients had received information regarding oral problems prior to or during treatment.

Paper II:

- To assess and examine oral health and adverse effects in palliative care cancer patients with cancers outside the head and neck region.
- To investigate if the palliative care cancer patients had received information regarding oral problems prior to or during treatment.

Paper III:

- To assess and examine oral health and adverse effects in long-term survivors of acute lymphoblastic leukemia treated with chemotherapy in Norway, with an emphasis on assessing if age at diagnosis and treatment related factors were associated with dental developmental defects.
- To assess the survivors' annual expenses for dental treatment compared with reference data.

MATERIALS AND METHODS

Study design

All three studies had a cross-sectional, descriptive design with data collected through questionnaires, semi-structured interviews, the Edmonton Symptom Assessment System (ESAS) (141, 142), and clinical and radiographic examinations. An overview of the study design as it pertains to papers I-III is provided in Table 5.

Table 5. Study design and measures

Paper	Design	Measures
I	Cross-sectional, descriptive study using a convenience sample	ESAS Semi-structured interview Clinical examination
II	Cross-sectional, descriptive study using a convenience sample	ESAS Semi-structured interview Clinical examination
III	Cross-sectional, descriptive, and comparative study All survivors of childhood acute lymphoblastic leukemia treated at OUH. Stratified random sample used to pick references.	Questionnaire Semi-structured interview Clinical examination Radiographic examination

ESAS: Edmonton Symptom Assessment System (141, 142), OUH: Oslo University Hospital

Subjects

In study I, a convenience sample of 226 outpatients receiving chemotherapy for cancers outside the head and neck region were invited to participate with inclusion once a week at the Cancer Center, Oslo University Hospital (OUH), Ullevaal. The inclusion criteria were: 1) a diagnosis of cancer outside the head and neck area, 2) receiving curative or adjuvant chemotherapy at the time of the study in an outpatient setting, 3) age 18 years or older, 4) ability to provide informed consent, and 5) cognitive and physical ability to undergo study procedures. Exclusion criteria were as follows: 1) cancer in the head and neck region, 2) radiation treatment to a metastasis in the head and neck region, and 3) not willing or physically/cognitively able to undergo all parts of the study protocol. Of the 226 patients who were approached, 155 patients (69%) completed the study (Table 6).

In study II, a convenience sample of 126 PC cancer inpatients were invited to participate with inclusion once a week at the Cancer Center, OUH, Ullevaal and at Hospice Lovisenberg, Oslo, Norway alternately. The inclusion criteria were (1) a diagnosis of advanced cancer outside the head and neck region, (2) admittance as a PC inpatient, (3) age ≥18 years, (4) ability to give informed consent, and (5) cognitive and physical ability to complete the questionnaire as judged by the patient's attending physician, based on standard clinical criteria; disturbed consciousness, disorientation to time/place and attention deficits. Of the 126 patients who were approached, 99 patients (79%) were included in the study (mean age 64, range 36-90, 47% males) (Table 6).

In study III, the Cancer Registry of Norway (http://www.kreftregisteret.no/en/) identified all adult survivors (≥18 years) of acute lymphoblastic leukemia treated before the age of 16 at OUH during the period 1970-2002 (n=210). Hence, all survivors were from the southeastern regions of Norway. Exclusion criteria encompassed radiotherapy, unwilling or unable to complete all parts of the study, or a condition interfering with dental development. Of the 210 survivors invited, 111 (53%) were included (Table 6). An age and region matched reference population was drawn from the survey of level of living in Norway (2008) (143, 144) with five references for each survivor (n=555) based on 5-year age groups of survivors. Cancer survivors were excluded prior to drawing the references based on the 10th revision of the International Classification of Diseases (ICD-10) diagnoses registered in the survey.

Table 6. Inclusion and patient characteristics in studies I-III

Inclusion	**Study I**	**Study II**	**Study III**
Subjects approached to participate, n (%)	226 (100)	126 (100)	210 (100)
Subjects who were excluded, n (%)	13[a] (6)	0[b] (0)	49[c] (23)
Subjects who declined, n (%)	58 (26)	27 (21)	50 (24)
Subjects included in the study, n (%)	155 (69)	99 (79)	111 (53)
Characteristics			
Female gender, n (%)	103 (67)	53 (54)	61 (55)
Age at examination (years), mean (SD)	57.0 (11.8)	63.9 (12.3)	29.1 (7.2)
Smoker, n (%)	23 (15)	25 (25)	23 (21)
Karnofsky Performance Status score[d] ≤40, n (%)	4 (3)	52 (53)	[e]
Regionally advanced or metastatic, n (%)	131 (85)	99 (100)	[e]

[a] Died during the time between their acceptance and the examination date. [b] Not applicable as a physician screened all the patients before inclusion. [c] Due to a diagnosis that can interfere with tooth development, having received radiation therapy, or not completing the study protocol. [d] Signifying a patient who is unable to care for self; who requires equivalent of institutional or hospital care; and where disease may be progressing rapidly (145, 146). [e] Not applicable as the study subjects are long-term survivors.

Registration forms and questionnaire

ESAS

All patients in studies I and II completed the Norwegian version of the ESAS (141, 142). The ESAS was designed for quantitative assessment of the intensity of the most common cancer symptoms with minimal patient burden and is among the most frequently used symptom assessment tools in advanced cancer and PC (141, 147). The modified Norwegian version used in the present study included 10 common symptoms of advanced cancer (pain at rest, pain when moving, fatigue, nausea, dyspnea, xerostomia, appetite, anxiety, depression, and general well-being) (142). The time frame of the symptom assessment is "now" (141, 148). All symptoms were scored on a 0–10 numerical rating scale, with higher scores implying higher symptom intensity.

Evaluation of general condition

In studies I and II Karnofsky Performance Status (KPS) (145, 146), hydration, weight loss was evaluated for all patients. Further, one of two experienced PC physicians assessed the patients' life expectancy in study II.

The KPS is a scale developed to rate physical function and dependence on help in cancer patients (145). The KPS scale includes 11 categories ranging from 0 (dead) to 100 (normal, no complaints, no evidence of disease), and has been shown to have good reliability (produce consistent and repeatable results) and validity (measures what it claims to measure) when evaluating performance status in cancer patients (145, 146). It has three larger subcategories: unable to care for self (KPS score: 0-40), unable to work (KPS score: 50-70), and able to carry out normal activity and to work (KPS score: 80-100) (145, 146).

A scale with the categories normal hydration, moderate dehydration or severe dehydration was used to evaluate hydration status. In study I, this was done by a clinical assessment of if pinched skin sprang back immediately (normal), tented briefly (moderate), or if there was a prolonged tenting (severe) (149). This test does not have great sensitivity (ability to identify dehydrated patients correctly) by itself, but has a positive predictive value of about 60% (percentage of positives that are dehydrated) (149). Conversely, the test has a very high specificity (ability to identify patients without dehydration correctly) and negative predictive value (percentage of negatives that are not dehydrated) (149). Similarly, weight loss was assessed using a four-point categorical scale with the categories: no, <5 kg, >5kg, and >10 kg of weight loss within the last six months. This scale reflects various definitions of cachexia (involuntary weight loss due to cancer) that range from 5-10% weight reduction in the last six months (150). In study II, an experienced PC physician evaluated these variables and life expectancy based on clinical evaluation and the patient's medical history.

Registration form

In paper I and II, a face-to-face registration form from an earlier pilot study on oral discomfort in cancer patients at OUH was used for the semi-structured interview (unpublished data; Herlofson BB poster presentation, European Association of Oral Medicine, Berlin 2004). The registration form included items on gender, age, nationality, previous and current disease, cancer diagnosis and treatment, medication, tobacco and alcohol use, oral care, oral problems, and whether information about oral issues was received by the patient before and/or during treatment. General oral discomfort was assessed by the question ‘‘Do you presently suffer from discomfort or pain from the oral cavity?’’. Further questions regarding oral symptoms included: “Does your mouth often feel dry?”, “Is food intake difficult?”, and “Does food and drink taste different than usual?”. These questions had dichotomous answer categories. The number of medications per patient were counted and grouped according to registered oral adverse effects such as mucositis, xerostomia and taste changes according to multiple national and international databases for drug information (70-72).

To compare the annual cost of dental services experienced by survivors to a reference population in study III the survivors received a mailed questionnaire including 143 items for men and 155 items for women as part of a multi-center study that included several different health professions. The reference population took part in a nationally representative survey Statistics Norway regularly perform in the population aged 16 or older (n=10,000)(143). The 2008 survey focused on health issues, including self-reported oral health as well as the cost and use of dental services (143). The Norwegian Centre for Research Data provided data from the national survey for the study. The items included in the questionnaire and national survey covered a wide range of themes where we had access to the items concerning annual cost of dental services, use of dental services, and self-evaluation of oral health as well as demographic, general health data, and treatment protocols (only survivors). The items concerning self-reported oral health and use of dental services in the questionnaire were identical to items the reference population answered in the national survey. However, in the national survey the participants provided the exact annual cost of dental services, which we converted into a categorical scale identical to the one included in the questionnaire filled in by the survivors prior to analysis. During the examination of the survivors, a registration form that included items on oral care and oral problems (e.g. survivors’s perception of xerostomia, taste disturbances, problems eating, reason for loss of teeth, and reflux at the time of the examination) was used.

Oral examination

In studies I and III the clinical oral examinations were conducted in a hospital examination room. In study II the clinical examination was performed at the bedside. Hence, none of the study subjects were examined in a dental office with access to e.g. intraoral x-rays. Systematic registrations of findings on teeth, gingiva, and oral mucosa were performed. Further, no clinical examination of the reference population in study III was possible.

Teeth

Registrations on the teeth in all of the studies included the number of remaining teeth, as well as caries experience which was evaluated using the DMFT index (151, 152). The wisdom teeth were not included in the analyses. The DMFT index records the number of teeth with either active or treated caries lesions. A tooth was registered as decayed if caries involved dentin or if secondary caries was found. In study III we additionally registered the number of 1) teeth that had not developed (i.e. hypodontia); 2) markedly smaller teeth (i.e. microdontia), 3) teeth with enamel hypoplasia (diagnosed as notches on the proximal surfaces), and 4) teeth with tooth wear. Hypomineralization was not included because it is difficult to distinguish this condition from other lesions given that the examinations were conducted outside of a dental office.

Plaque and periodontium

In studies I and II dental plaque and gingival health were evaluated using the mucosal-plaque score (MPS) index developed for the evaluation of oral health and hygiene in hospitalized and nursing home patients (153). In study III dental plaque and gingival health were registered according to a commonly used index developed by Löe (154). Further, in all three studies dental plaque was dichotomized into no/small amount or moderate/large amount of dental plaque. Gingival health was dichotomized into bleeding on probing or not for analyses.

Oral mucosa

Examination of the oral mucosa in all three studies included signs of 1) infections (e.g. candidiasis), 2) toxic effects (e.g. mucositis), 3) conditions associated with the immune system (e.g. lichenoid reactions), and 4) traumatic injury (e.g. cheek biting). Oral candidiasis was registered according to the classification proposed by Axell and co-workers (155), and oral mucosal swabs were taken from the tongue and buccal vestibule for possible identification of fungal carriage. The WHO's classification system for mucositis (56, 156) was used.

Radiological examination

In studies I and II no previous radiographs were available, and no new radiological examinations were performed.

In study III a panoramic radiograph was taken of all of the survivors and examined for short roots, microdontia, hypodontia, and other oral malformations and diseases.

Root-crown ratio

A method first described by Volmer Lind for the measurement of the root-crown ratio (RC) of maxillary incisors (157) and later adapted to the full dentition by Hölttä and co-workers (158, 159) was used to measure and calculate the RC as a measure of arrested root development (Figure 1).

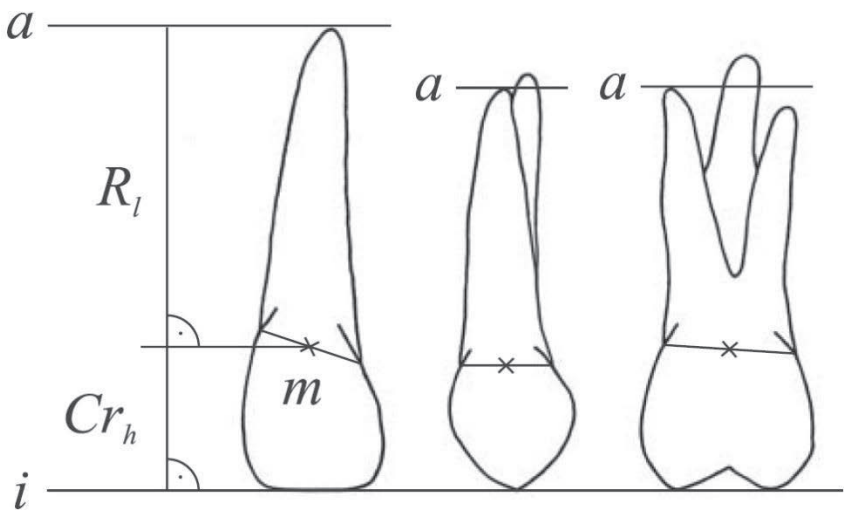

Figure 1. How the height of the crown (Cr_h) and the length of the roots (R_l) were measured on the panoramic radiograph for the different tooth groups. The apical tangent of the longest buccal root was designated as *a*, the incisal/occlusal line was designated as *I*, and *m* was the visually determined midpoint of a straight line connecting the points of intersection between the contours of the root and crown (159). (Reprinted with the permission of the Rights Department of Oxford University press©)

All teeth except the wisdom teeth were assessed to determine if the RC measurement was possible, but excluded from measurements if: 1) the apex was not closed, 2) reference points were not visible, 3) the roots deviated markedly from the tooth axis, 4) there was a history of dental trauma, 5) marked tooth wear affecting the reference points was present, 6) microdontia was present, 7) hypodontia was present, and 8) teeth were missing for other reasons. All measurements were performed by two independent dentists who prior to the study had shown acceptable inter- and intra-rater reliability (160) when measuring the RC. The mean RC values of the two raters' individual measurements were used in the final analyses.

Individual defect index

The Individual defect index (IDeI) was introduced by Hölttä in her thesis from 2005 (158) and is an amendment of a previous defect index (DeI) (161). The IDeI is an index based on assessment of a subject's teeth on a panoramic radiograph and the assignment of defect points to each tooth according to three major developmental aberrations: 1) arrested tooth development expressed through a z-score showing how much a subject's RC deviates from a gender specific mean value from a healthy reference population, 2) microdontia, and 3) hypodontia (Table 7). The subject's overall dental aberrations are then expressed as a compound score between 0 (no developmental disturbances) and 140 (anodontia—all teeth failed to develop).

The z-score (z) used to indicate how much an individual's RC deviated from a healthy reference population was calculated for each tooth using the following formula:

$$z = \frac{RC_{survivors} - RC_{mean}}{SD}$$

Previously published tooth- and gender-specific RC_{mean} and standard deviation (SD) values from a healthy Finnish population were used in the calculation of the z-score (159).

Microdontia was recorded when a tooth was markedly smaller than expected for the tooth group in question.

Hypodontia was recorded when survivors specifically remembered that a tooth never developed or when this was obvious on the radiographs.

Table 7. How points are assigned in the individual defect index

Dental defect measured	z-range	Defect points
Hypodontia		5
Microdontia		4
Root-crown ratio:	$-2 \leq z \leq 2$	0
	$-3 \leq z < -2$ or $2 < z \leq 3$	1
	$-4 \leq z < -3$ or $3 < z \leq 4$	2
	$-6 \leq z < -4$ or $4 < z \leq 6$	3
	$-6 > z > 6$	4

z: The z-score indicate how much a study subject's root-crown ratio deviates from the mean value of a reference population, expressed as units of the standard deviation in the reference population (158).

Statistical analyses

The statistical analyses were based on the answers and findings recorded from the questionnaires, clinical examinations, and radiological examinations. The software SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for data analysis in study I. In studies II and III, the IBM SPSS Statistics software for Windows, versions 20 and 22, (IBM, Armonk, NY, USA) were used respectively. A p value of 0.05 or less was taken to indicate statistical significance. The statistical methods used in the different studies are shown in table 8.

Table 8: Statistical methods used

Study	Statistical methods
I	Independent-samples t-test Chi-square test *t*-test One-way analysis of variance (ANOVA) with a post hoc Tukey HSD Multivariate logistic regression
II	Independent-samples t-test Chi-square test *t*-test Multivariate logistic regression
III	Independent-samples t-test Chi-square test *t*-test Spearman correlation One-way analysis of variance (ANOVA) with a post hoc Tukey HSD Unadjusted and multivariate linear regression

In studies I and II the variables were described by means, standard deviations and percentages. The dependent variable, oral discomfort, was determined by the patients' answer to the dichotomous question: "Do you suffer from discomfort or pain from the oral cavity at present? Yes/No". The significant factors associated with oral discomfort in the univariate analyses were entered as predictors in multivariate logistic regression models.

In study III the variables were described by means, standard deviations, medians, ranges, and percentages. Dichotomization was performed on several variables prior to analyses. The IDeI score was used as the dependent variable in the linear regression analyses.

Ethical considerations

The Regional Committee for Medical and Health Research Ethics of South East Norway approved all three studies. All patients provided written informed consent. Due to altered regulations for ethical approval of research studies in Norway during the completion of this PhD project, studies I and II had additional approvals showing that data storage and conduct of the study were performed according to the regulations set forth by the Norwegian Data Inspectorate, the Data Protection Supervisor and the Research Committee at OUH.

RESULTS

Paper I: Chemotherapy-associated oral sequelae in patients with cancers outside the head and neck region

All patients (n=155) had solid organ cancer with breast (45%), gastrointestinal (37%), and prostate cancer (7%) being the most prevalent diagnoses. The majority of patients (85%) had regionally advanced and/or metastatic disease.

The most frequently reported oral problems among patients who reported discomfort (n=64, 41%) were xerostomia (82%) and taste changes (75%). At the time of examination, 16 (10%) patients had both clinical and microbiological evidence of oral candidiasis. Mucositis grade 1-2 were seen in 18 patients (12%).

A higher proportion of patients who reported oral discomfort scored >3 on the ESAS xerostomia item compared to patients who did not report oral morbidity (61% vs. 21%; $p<0.001$). Further, they also reported a significantly higher mean intensity on the ESAS xerostomia item [4.7 (SD: 2.6) vs. 1.9 (SD: 2.5); $p<0.001$] and were taking significantly more systemic medications than patients who did not experience oral discomfort [6.4 (SD: 2.6) vs. 5.3 (SD: 2.4); $p=0.01$].

Only 27% of the patients stated that they had received information about possible oral adverse effects related to cancer and cancer treatment, or about the importance of maintaining good oral hygiene during treatment. Among the 92 (59%) patients reporting xerostomia as a problem, only 31 (34%) patients said that they had received information about measures to reduce symptoms of xerostomia.

The ESAS item xerostomia >3 ($p<0.001$), mucositis ($p=0.03$), and a higher number of systemic medications ($p=0.03$) were significantly associated with more oral discomfort in the multivariate analysis.

Paper II. Oral health is an important issue in end-of-life cancer care

Among the 99 patients included in this study, gastrointestinal cancer (21%), lung cancer (19%) and prostate cancer (11%) were the most prevalent diagnoses. Patients had a median KPS score of 40 (range: 20-80), and all patients had either locally advanced or metastatic disease. Seventy-three percent of the patients died within 3 months of examination.

The most frequent oral problems among the patients who reported discomfort (n=66, 67%) were xerostomia (94%) and taste changes (80%). Patients who experienced oral discomfort also reported high symptom distress from xerostomia on the ESAS (mean 5.7, SD 2.6). At the time of examination, 34 (34%) patients had both clinical and microbiological evidence of oral candidiasis. The mean DMFT for the entire patient group was 20.7 with 51% having decayed teeth.

Only 22% of the patients stated that they had received information about adverse effects in the oral cavity caused by cancer and cancer treatment, whereas 31% said they had received information about the importance of oral hygiene during treatment. Among the patients who reported xerostomia as a problem, 43% had received information about measures to reduce symptoms.

Xerostomia ($p<0.001$) and taste alterations ($p=0.03$) were significantly associated with oral discomfort in a multivariate analysis.

Paper III: Dental abnormalities after chemotherapy in long-term survivors of childhood acute lymphoblastic leukemia; 7-40 years after diagnosis

The mean age of the 111 survivors at the time of the survey was 29.1 years (SD 7.2) with a mean age at diagnosis of 6.2 years (SD 4.1). The median follow-up period was 23.4 years (range: 7.4-40.2 years). Relapse had been diagnosed in nine (8%) of the survivors, with two (2%) survivors receiving allogeneic HSCT after relapse.

The mean IDeI score among survivors was 13.7 (SD 11.7). The age at diagnosis (B =−9.6, $p<0.001$) and treatment with anthracyclines (B=11.5, $p<0.001$) were significantly associated with the IDeI in the multivariate analysis. Out of the 31 (28%) survivors registered with microdontia, 29 (94%) had been diagnosed at the age of 5 or less. Enamel hypoplasia was also registered to a larger degree in survivors diagnosed at the age of 5 or less compared to survivors who were older when diagnosed (76% vs. 18% respectively; $p<0.001$). The IDeI RC component score was >0 for one or more teeth in 92% of the survivors.

Survivors diagnosed at the age of 5 or less had a significantly lower mean DMFT compared to survivors diagnosed after the age of 5 [6.0 (SD 4.6) vs. 9.6 (SD 6.1) respectively; p=0.001].

A high annual cost for dental treatment was reported by ten survivors (9%), and was significantly associated with a high mean DMFT compared to survivors with no or low cost [mean DMFT (SD): 12.4 (6.5) vs. 7.4 (5.5) respectively; p=0.01].

When comparing survivors and references who reported having expenses within the last year, no significant difference was found; as the percentages who reported high expenses for dental treatment were 14% vs. 21% respectively (p=0.22). Further, no significant differences were observed in the percentage of survivors who sought dental services annually compared to the reference group (68% vs. 65% respectively; p=0.43) or who self-evaluated their oral health as poor (11% vs. 7 % respectively; p=0.15).

DISCUSSION

Methodological considerations

Subjects

In papers I and II we used convenience samples of cancer patients who were either receiving chemotherapy in an outpatient setting (Paper I) or admitted to one of two PC units (Paper II). In paper I, the main reason for doing this was that the examination room at the hospital was only available to us at a given time every week. There is a risk of introducing a selection bias when using this method, e.g. if patients who were treated during the available time slot differ from patients treated on other days with respect to diagnosis, stage of disease, treatment regimen etc. Hence, if the patients treated outside of our time slot, differed from the included patients with respect to such variables, we may have under- or over-estimated oral health problems in our study. We did not have access to any data regarding patients treated outside of the time slot where we could interview and examine patients. Consequently, we cannot rule out the possibility of a selection bias in the material. However, we tried to minimize selection bias by inviting all patients who fulfilled the inclusion criteria in a consecutive manner.

In paper II, the choice to use a convenience sample including new patients every 14 days alternately between the two PC units, was based on the expected turnover of patients as stated by the attending physicians. Again, patients who fulfilled the inclusion criteria were invited in a consecutive manner to reduce the risk of selection bias. However, this selection method entails that we may have missed some patients with very short admissions to the PC units. Consequently, the same reservations apply to paper II as paper I regarding bias in the patient selection. It is a limitation to both these studies that they do not contain a reference population. However, the aims of both studies were to assess oral health and if information was received in Norwegian patients receiving chemotherapy and/or symptom management.

In paper III, all long-term survivors (≥18 years of age) who received treatment at OUH between 1970 and 2002 for acute lymphatic leukemia during childhood and adolescence (<16 years of age) were included. We found no significant differences regarding age at diagnosis or gender between the included survivors and the non-responders or excluded patients. OUH provides care for children and adolescents with acute lymphoblastic leukemia from the south-eastern part of Norway. The population of the south-eastern part of Norway is about 2.8 million people (approx. 56% of the total population). The treatment protocols for acute lymphoblastic leukemia are the same in all of the Nordic countries. Hence, it is reasonable to assume that our sample is representative for long-term survivors of acute lymphoblastic leukemia treated in the Nordic countries. However, the non-responders and excluded survivors may differ from the included on e.g. socio-economic or health-related factors, or other unknown factors that may cause bias in our study. Low annual income and

education, and poor general health are associated with poor oral health in Norway (144). Hence, if the non-responders differed from the included survivors with respect to such variables, we may have under- or over-estimated oral health problems in our study.

The age and region matched reference population in paper III was randomly selected from a nationally representative population survey conducted by Statistics Norway in 2008, focusing on health issues including self-reported oral health. As mentioned above, many of the oral health items in this study matched the items included in the questionnaire filled out by the survivors prior to examination. This enabled us to compare self-reported oral health, number of visits to dental services within the last year, and annual expenses for dental care. However, there was a large discrepancy in the response rate concerning annual expenses (100% among survivors vs. 63% among references) making comparison of the two groups difficult. Further complicating this is that among the 37% of the references who did not provide information regarding annual expenses, 11% considered their oral health to be poor (not reported in Paper III). Some ways of interpreting this are that 1) they have little annual expenses, but did not report them regardless of treatment needs; 2) they have high expenses, but did not report them; or 3) they do not visit dental services to the same degree as others (only 8% of them had visited the dentist within the last year, and 41% had not received dental services within the last two years). Regardless of which explanation is more likely, the missing values in the reference population have likely influenced the results regarding annual expenses to a large degree. A major limitation was that we did not have clinical examinations or radiographs of the references and could not compare e.g. developmental disturbances, caries experience or periodontal health. However, a recent review provided some information regarding oral health in survivors of ALL treated with chemotherapy compared to references from the general population (139). Hence, our study provide new information about such patients, and complements earlier research that has focused on survivors who have received total body irradiation or HSCT as well as those with heterogeneous diagnoses and/or shorter follow-up times (35, 42, 43, 45-48, 53, 54, 107, 139, 158, 162-164).

Registration forms and questionnaire

In paper I and II a face-to-face registration form developed by the investigators and used in a previous pilot study on oral morbidity in cancer patients at OUH, was used for the semi-structured interview. The form included KPS and the Norwegian version of the ESAS, which included an item on xerostomia and was in clinical use at the PC units at OUH and Hospice Lovisenberg at the time of the studies. However, after the closure of our studies a revised version of ESAS was developed and subsequently translated into Norwegian (148, 165). This revised version does not include an item regarding xerostomia, but contains an open tenth item labeled "other problem (for example constipation)". Accordingly, patients may include xerostomia as the open item, but it is unlikely due to the use of constipation as an example in populations where opioids abound. Hence, the ESAS likely will not be used extensively for symptom assessment in future studies concerning oral health. The time frame "now" used with the ESAS, referring to the situation at the time of assessment, can be viewed both as a strength and a limitation of the method. An alternative symptom assessment scale we could have used is the Memorial Symptom Assessment Scale (MSAS), which has the time frame of "during the last week" (166). Advantages of this scale are that it includes several items concerning oral health, covers the most frequent symptoms associated with cancer treatment, and was constructed to assess symptoms in both out- and inpatients (166, 167). However, this scale was not translated into Norwegian at the time of the study and requires more time to fill in than the ESAS. We did not include any instruments for measuring QoL in this thesis. Instruments such as the Short Form 36 Health Survey (SF-36) (general health related quality of life) (168-171) and/or the Oral Health Impact Profile-14 (OHIP-14) (oral health related quality of life) (172, 173), both with acceptable validity and reliability, would have enabled comparison to other QoL studies and increased the value of our data (168-173). However, both of these instruments, as well as the European Organisation for Research and Treatment of Cancer (EORTC) Head and Neck module (the EORTC QLQ-H&N35) that contains several items related to oral problems (174), were reviewed when developing the registration form. In retrospect, the inclusion of the two former instruments would have increased the generalizability of our results.

In paper III, the survivors received an extensive, mailed questionnaire as part of a multi-center study. This questionnaire included ten oral health related items. As mentioned above, several items matched items in the national survey filled in by the references, enabling comparison of the two groups with regard to some self-reported oral health issues and demographic characteristics. However, the response rate regarding annual expenses for dental services was low among the references, reducing the value of the comparison of the two groups.

Response rate

In papers I and II, the completion rate of the study protocols were 69% and 79% of the invited patients respectively. A response rate below 60% to health questionnaires has been postulated to be too low for publication in some biomedical journals (175). Hence, the response rate in papers I and II may be considered as good. In paper III the proportion of invited survivors who completed the study was 53%. However, this percentage is derived from all the 210 survivors of ALL regardless of whether they were eligible for the oral health study according to inclusion and exclusion criteria. When applying these criteria, 21 survivors were excluded due to radiotherapy or having a diagnosis that can interfere with tooth development. This imply that compliance was 59% assuming all non-responders and those who declined participation fulfilled the inclusion criteria (111 survivors completed the protocol of the 189 eligible). Further, we did not have access to other treatment related items than age at diagnosis for the 50 non-responders. This may have resulted in a selection bias, e.g. if the non-responders had received radiotherapy to a lesser or higher degree than responders. However, the non-responders did not differ significantly from the included patients with regard to gender or age at diagnosis. This makes it reasonable to conclude that the sample was representative for the survivors of acute lymphoblastic leukemia treated before the age of 16 years at OUH between 1970 and 2002.

Clinical/radiological examination

The clinical examinations in papers I and III were conducted in a hospital examination room whereas a bedside examination was conducted in paper II. In papers I and II, no radiological examinations were available. In paper III, a panoramic x-ray was taken of all included survivors.

In both papers I and II, oral examinations were carried out using a headlamp as the light source due to the furnishings of the examination rooms. In paper III, a surgical lamp was used as the light source. Ideally, all examinations should have been conducted in a dental office with good light, all examination tools at hand, and a good ergonomic position for the examiner. However, neither of the sites where the examinations were conducted has such facilities, nor was moving the patients to e.g. the dental faculty for examinations an option given the included populations. To a degree, the examination conditions dictated the choice of indexes and tools used for registration of oral findings. For example, caries experience was registered according to the DMFT index (151, 152) in all three papers, where a decayed tooth was registered when a carious lesion reached dentin. Consequently, registration of enamel caries (and enamel hypomineralization) was not included in these studies and the lack of x-rays may have led to an under-registration of small approximal cavities and filled teeth. However, our examinations likely registered carious lesions that needed treatment.

In papers I and II, plaque and gingival health was recorded according to the MPS index which was developed for evaluation of these items in hospitalized patients (153), whereas in paper III we were able to use indexes more common in dental practice (154). However, both methods of registering gingival health made it possible to further dichotomize the scores into bleeding on probing or not in all three papers (bleeding on probing is called moderate/severe gingivitis in Papers I and II). However, the lack of intraoral x-rays may have led to an underestimation of marginal periodontitis in our studies.

Mucositis was graded according to WHO classification system due to its ease of registration and widespread use in research and clinical practice in Norway and internationally, which increases the generalizability of our results (156). Although widely used, a limitation of the WHO grading system is that it combines symptoms (pain), signs (erythema and ulcerations), and functional problems (type of diet the patient is able to tolerate) (56). There is a multitude of other assessment tools available for mucositis and e.g. the 20-item Oral Mucositis Index (176) or the Oral Mucositis Assessment Scale (177) would have enabled a more precise and quantifiable mucositis assessment. However, our objective was not to quantify mucositis, but to assess the prevalence and how it was related to the patients' self-reported oral discomfort.

Candidiasis was registered clinically according to the classification set forth by Axell and co-workers (155) and confirmed with culture from oral swabs. Culture was used to provide data regarding candida-carriage. In both paper I and II, Sabouraud's dextrose agar was used for inoculation. This agar does not have any chromogenic properties that can differentiate

different candida species and further microbial or resistance tests were not performed. Consequently, we were not able to identify different species of candida in our study, or provide a complete explanation for persisting candidiasis observed in patients already receiving antifungal therapy. In retrospect, the use of a chromogenic agar and identification and resistance testing of yeasts using laboratory techniques would have increased the clinical and research value of the oral swab.

In paper III the dental developmental defects microdontia, hypodontia and arrested root development were based on the panoramic radiograph according to the method described by Hölttä (158). Enamel hypoplasia was recorded clinically. Hypomineralization was not registered, as it is difficult to distinguish from other lesions. Microdontia and hypodontia was recorded clinically in addition to the radiological registration, with hypodontia also being registered anamnestically under certain conditions (if the patient had a very clear recollection of e.g. missing teeth that had been orthodontically compensated for). This element introduced the risk of recall bias in the recording of especially hypodontia in this study, which in turn carries the risk of misclassification. Hence, missing teeth where a survivor thought it had never developed or was uncertain, would be registered as missing due to "other reasons" to reduce the risk of erroneous recording of a tooth as developmentally missing when it was not. Because of the decisions made to avoid registering healthy teeth as teeth with defects, we most likely underestimated the number of developmentally missing teeth, microdontic teeth, and teeth with mild or treated enamel hypoplasia. However, this does not seem to be a major issue as our results is in line with what has been reported from other studies (42, 139, 178).

We decided to use IDeI as our main scoring system for developmental disturbances in paper III (158). This is a relatively new scoring system, and is based on examination of and measurements on a panoramic radiograph. An advantage of this method is that the scoring of arrested root development is based on objective measurements instead of the subjective assessment used in other systems (53, 162). This selection made it possible to compare our findings with a published Scandinavian reference material, which we consider a major advantage (159). These advantages facilitate evaluation of the smaller deviances from normal root development that we expected to find in survivors treated with chemotherapy only. There are several limitations to the IDeI. The method is very time consuming with calibration of the raters, measuring all the teeth, calculation of z-scores, and assigning defect points before analysis can begin. Further, it would be preferable with measurements from a Norwegian reference population, but tooth development patterns differ little within Caucasians (179), and we do not consider the use of a Finnish reference material to be a major limitation of the study. In the IDeI, evaluation of microdontic teeth is based on the raters' subjective opinion and only includes very small teeth, and no score is assigned to some dental developmental defects such as enamel hypoplasia. Therefore, we registered enamel hypoplasia clinically and reported our findings to provide a more complete picture of the developmental disturbances found in the survivors. Other systems used for registering

and/or scoring developmental disturbances in cancer survivors include enamel hypoplasia, but have other limitations. One such system was proposed by Dahllöf and co-workers in 1988, and is based on a combined assessment of clinical (enamel hypoplasia diagnosed as notches on the proximal surface) and radiological findings (short, v-shaped roots and premature closure of the roots), and microdontia is recorded (162). This system does not involve a scoring system, but is a registration of four different developmental defects. Sonis and co-workers further developed this registration tool, including more types of defects (added categories for severely stunted roots, anomalies in root number, and agenesis) and assigning severity scores to the different defects (53). The scoring system enabled an easier comparison of defects across different patient populations. However, both of these systems rely heavily on subjective interpretation of the dental defects, as they do not propose any root or crown measurements or definition of microdontic teeth, nor do they propose any comparison to a reference population (53, 162).

Discussion of major findings

The main objective of the present study was to investigate the subjective and objective oral adverse effects in cancer-patients treated with chemotherapy for cancer outside the head and neck region at different phases of the disease trajectory. Further, we aimed to assess if the patients had received information regarding oral problems prior to or during treatment, and the annual expenses for dental treatment reported by survivors of ALL in childhood.

Self-reported oral adverse effects

Oral Pain

Oral pain was not directly assessed in our studies, but was included in the question relating to oral discomfort. Hence, oral pain and sub-classification of different categories of pain (e.g. nociceptive or neuropathic) were not reported. However, we assessed factors associated with orofacial pain (e.g. mucositis and oral infections) (180). The lack of pain assessment is a limitation in our studies which could have been remedied by adding a visual analog scale or a numerical rating scale regarding orofacial pain to the registration form. Such an addition would have enabled a more complete representation of the patient's symptom burden However, the choice to bundle discomfort and pain in one question enabled an assessment of if the patients' were bothered by any oral symptoms. Hjermstad and co-workers on behalf of the EORTC, recently published a quality of life module for oral health (the EORTC QLQ-OH15) (181) validated for use in heterogeneous cancer populations, at different disease stages and in different cultural settings. This module is to be used together with the EORTC core questionnaire (the EORTC QLQ-C30) (182). These questionnaires address both general and oral quality of life, with the oral health module assessing i.e. oral discomfort, oral pain, problems with dentures, information variables, and how this influences quality of life (181). The brevity of the module makes it a feasible and relevant tool to include in clinical trials and follow-up studies and may direct more focus to oral problems related to different cancer diagnoses and treatments.

Xerostomia

The prevalence of xerostomia reported in papers I-III does not differ much from other studies. In a review conducted on behalf of the MASCC / ISOO oral health study group in 2010, Jensen and co-workers reported a weighted prevalence of xerostomia of 50% during chemotherapy (31). We reported a prevalence of xerostomia in patients receiving chemotherapy of 59%, with 37% grading the symptom intensity greater than 3 on the ESAS (Paper I). Among cancer patients admitted to PC units, the prevalence of xerostomia has been reported to range from 67%-82% (10, 12, 183). In paper II, we reported a prevalence of xerostomia of 78% among PC patients. In paper III, xerostomia was reported by 23% of the survivors of childhood acute lymphoblastic leukemia, which is within the range of 5-39% reported for the general public (184). Further, this study showed that xerostomia is significantly associated with self-reported oral discomfort in both outpatients receiving

chemotherapy and in PC cancer patients. In both groups, xerostomia was the symptom with the highest symptom intensity score on the ESAS among patients who reported oral morbidity. It was rated second highest (after fatigue) if all patients were considered (Papers I and II). This does not necessarily mean that xerostomia bothers patients the most during chemotherapy or PC, but it is a persisting symptom (especially in PC cancer patients) involved in the development/maintenance/enhancement of many other oral adverse effects. Hence, our results may reflect the difficulty of assessing and managing this symptom in a setting with limited or no access to oral health care professionals. However, a recent study evaluating oral problems before and after an intervention in 278 terminally ill Japanese cancer patients, showed marked improvement of severe xerostomia in PC patients with the use of relatively limited resources (183). They showed that routine use of a standard oral care protocol (including moisturizing agents, brushing of teeth, removal of plaque from the tongue, and oral massage) administered by the ward staff improved up to 67% of the most severe xerostomia cases (183). Further, they found that involving dental hygienists, dentists, and oral surgeons brought the improvement rate up above 80% for the most severely affected patients (183). In less severely affected patients they had even higher improvement rates (183).

Xerostomia is a common side effect of many common drug classes used in cancer treatment and PC, but can be further exacerbated by the use of multiple drugs concomitantly (i.e. polypharmacy) (184). Such exacerbations have been observed in randomized controlled trials to occur as early as with an increase from one to two drugs, and a further increase in the number of drugs will exacerbate the problem (184). This is in concordance with our finding in paper I, that a greater number of systemic drugs were associated with oral morbidity. In paper II we did not observe the same association between the number of systemic drugs and oral adverse effects. PC physicians re-evaluate all drugs the patients receive at admission resulting in a reduced number of drugs, but almost all patients still received many drugs when examined. This may explain why the number of drugs was not significantly associated with oral discomfort in study II, and indicate that some patients are more resilient to oral adverse effects.

Altered perception of taste

There are relatively few studies concerning taste changes experienced by cancer patients at different stages in the disease trajectory. However, taste alteration is reported to be a common adverse effect of both chemotherapy (approximately 56% during chemotherapy) and among PC patients (approximately 70 % in a PC setting) (110, 185). This is in accordance with the prevalence of taste changes of 62% among patients receiving chemotherapy (Paper I) and of 68% among PC patients (Paper II) reported in this study. In paper III the prevalence of taste alterations was not reported due to few survivors actually being able to answer this question (recall bias). The most common reasons for not replying to this question in study III were their age at treatment (very young) or the very long follow-up (could not remember how their sense of taste was prior to treatment).

Many of the drugs used in cancer treatment and symptom management have taste changes as a known adverse effect (Table 3). Our studies (Papers I and II) showed that significantly more patients who report oral discomfort also report taste changes compared to patients who do not report oral discomfort. Further, taste changes are a predictor of oral discomfort in PC patients (Paper II). Epstein and co-workers recently reported that taste alterations is very rare in the general population, but very common among cancer patients (186). Further, there is a need for more research using e.g. clinical taste testing procedures in cancer patients (186). This suggests that the relationship between taste alterations and oral discomfort/health in cancer patients should be explored further in future studies using different techniques, as taste changes may be a significant problem during cancer treatment with curative intent and in a PC setting.

Our results also suggest that the prevalence of taste alterations is lower among patients receiving a fluorouracil, epirubicin, and cyclophosphamide (FEC) chemotherapeutic regimen than other regimens (Paper I). FEC is a standard chemotherapeutic regimen given to breast cancer patients in Norway. This is in contrast to Bernhardson and co-workers who concluded that taste and smell disturbances were common across chemotherapeutic regimens (39). They further reported breast cancer and the female sex among the significant predictors of taste and smell changes (39). One possible explanation for this difference in results across the two studies may be that we only measured taste change, whereas Bernhardson and co-workers measured both taste and smell changes. Taste changes do not differ as much between sexes, whereas smell changes have been reported to affect females to a larger degree than men (39). Another explanation might be that we did not ask about specific types of taste changes. It is reasonable to assume that asking about specific taste changes might increase a patient's attention to the problem, and lead to a higher proportion of patients answering "yes" regarding this problem. This is a limitation to our study, but the less specific question used in our study likely enabled us to register the patients who considered taste changes a problem.

Swallowing dysfunction

Swallowing dysfunction was not specifically addressed in any of the studies included in this thesis. However, problems eating food was reported in papers I and II. This problem was not assessed in paper III. During treatment (Paper I), problems eating was significantly associated with oral discomfort and 27% of the patients reported this as a problem. Among the PC patients (Paper II), 56% reported having problems eating food, but there was no significant difference between those who reported oral discomfort and those who did not. This factor was a prevalent problem, but not a significant predictor of oral discomfort in paper I or II. Recent reviews have shown an increased risk of swallowing dysfunction during chemotherapy in advanced cancer patients (187) and a prevalence of between 8.5% and 40% of swallowing dysfunction during chemo- or chemoradiotherapy (36). The prevalence of 27% from paper I support these results. However, the high number of patients reporting this problem in the PC population (Paper II) likely reflect the complex symptom burden these

patients experience. A probable reason why problems eating was not a significant predictor of oral discomfort in our studies, could be that many other oral adverse effects such as mucositis, infection, xerostomia and taste changes contribute to experiencing problems with food intake to a large degree (36, 187). Further, other factors such as obstructions of the alimentary tract, nausea, depression, fatigue, and reduced appetite may further exacerbate problems with food intake.

Clinically/radiologically manifest oral adverse effects

Mucositis

In outpatients receiving chemotherapy, mucositis of WHO grade 1 and 2 was recorded in 12% whereas none of the patients had a higher grade (Paper I). Nevertheless, mucositis was a significant predictor of oral discomfort in this study (Paper I). The number of patients with mucositis was not reported in papers II or III.

During conventional chemotherapy approximately 40% of the patients will experience mucositis, and an increased risk of ulcerative oral mucositis during subsequent cycles has been reported in breast cancer patients (83, 188). Hence, both the prevalence and severity of this adverse effect reported in paper I is very low. However, this discrepancy is likely due to the timing of the oral examination and inclusion of many different treatment regimens in our study. Accordingly, it should not be concluded that Norwegian cancer patients tolerate treatment better than patients in other studies. We examined the patients when they were at the clinic to receive their next treatment cycle, and this corresponds to when the patient was deemed healthy enough to receive such treatment by their oncologist. Hence, patients with severe mucositis may have been evaluated by their oncologist as not eligible for their next treatment cycle, causing a selection bias in our data towards patients who had less severe oral symptoms. Interruption or postponement of therapy is a serious and well known consequence of mucositis which may reduce survival (189). Patients often reported that they had had more severe ulcerations in their mouth between treatment cycles. Hence, our findings correspond to the pathobiology of chemotherapy induced mucositis (ulcerations appearing approximately one week after infusion, which resolves within two weeks) (188). Our data support the results from other studies, that fluorouracil based regimens are associated with more mucositis than other regimens (56). A recent review article reported that mucositis also afflicts more than 20% of patients with advanced cancer in different PC settings with impairment of their nutrition and hydration (187). In retrospect, it would have been of great interest if we had reported our data on mucositis in paper II and subsequently evaluated its impact on oral discomfort in this patient population. However, our analyses showed no significant association between these variables in our study and they were not reported in the paper.

Oral infections

In the papers included in this thesis, we reported results regarding the oral infections candidiasis, caries and gingivitis. Although not reported, we observed one case of sialadenitis of a minor salivary gland in one of the PC patients, and mild viral infections (i.e. herpes labialis) were seen sporadically.

Candidiasis

Candida infections were recorded across all studies (Papers I-III), but the results were not presented in paper III as no survivors had manifest candidiasis. However, 37 (34%) of the survivors were candida carriers (not reported in Paper III). This is similar to the median prevalence (34%) and range of yeast carriage (3%-48%) reported in healthy adults (190). However, the prevalence of yeast carriage is highly dependent on the sampling technique, and recent studies using methods that are more advanced, have detected oral yeast carriage of 100% in healthy subjects (191, 192). The candida carriage rates reported in papers I and II (72% during chemotherapy and 86% in PC patients) are very similar to rates reported in other studies (73% during chemotherapy and 83% during PC) (32, 193). These results indicate that Norwegian cancer patients do not differ significantly from comparable patient groups internationally and that our results complement other studies regarding fungal carriage. However, the prevalence of candidiasis (10%) reported in paper I is much lower than the 38% reported in patients receiving chemotherapy by Lalla and co-workers in a recent MASCC / ISOO review (32). This discrepancy most likely reflects the different diagnoses and therapies included. In the review, all of the studies regarding fungal infections during chemotherapy were conducted in leukemia or lymphoma patients (32), whereas our study only included patients with solid organ tumors outside the head and neck. Further, a recent report from the French CANDISCOPE study show similar prevalence rates as found in our study for solid organ tumors (from 2% in pancreatic and prostate cancers to 20% in gastrointestinal cancer, and 8% for chemotherapy alone) (194). In paper II we reported a prevalence of candidiasis of 34% which is similar to prevalence rates reported in other studies conducted in PC patients (13%-48%) (124, 193, 195, 196). In the light of the discoveries regarding candida carriage in healthy adults (191, 192), the high rates of fungal infections and fungal carriage detected in cancer patients during chemotherapy and PC using less sophisticated methods are not surprising. It likely reflects the compromised immune system in these patient populations (e.g. loss of saliva's protective properties, reduced epithelial barrier function, and immunosuppression), which in turn may lead to opportunistic colonization and infection by commensal fungal species (197).

Caries

In papers II and III, caries was reported as caries experience using the DMFT index with mean DMFT scores of 20.7 (PC patients; mean age 64 years) and 7.9 (survivors after childhood ALL; mean age 29 years) respectively. Further, the percentage of patients with decayed teeth was reported for the PC patients (51%). The corresponding percentage of survivors with decayed teeth was 32% (not reported in Paper III). Diagnosis after the age of five was associated with

increased caries experience compared to those who were younger at diagnosis (DMFT: 9.6, SD 6.1 vs DMFT: 6.0, SD 4.6; p=0.001) in paper III.

Comparison to the Norwegian population:

In Norway, DMFT is recorded by the government from children and adolescents aged 5, 12 and 18 years examined or treated in the public dental health system. For adults no such registration is done and much less is known about adult dental health. However, there is a cohort study which includes DMFT in adults from the county North Trøndelag at four time points from 1973-2006 (198-200) and a series of cross-sectional studies (1973-2003) examining 35-year-olds in Oslo (198, 201). Both of these study series show a marked decrease in mean DMFT over time in Norway, with a mean DMFT of 11.7 among 35-year-olds in Oslo in 2003; and 14.0 among the age group 35-44 years, 16.4 among the age group 46-47 years, and 23.7 among the age group 68-77 years in North Trøndelag in 2006 (198-201). One study has investigated the trends in Norwegian DMFT-data and stipulated that an increase of 0.15 (1.6%) in DMFT every year seems to be an appropriate estimate for the whole country (202). When all this is taken into consideration, the mean DMFT reported in papers II and III indicates that the caries experience in PC patients and long-term survivors after ALL does not differ much from the rest of the Norwegian population. This is further supported by the results reported in paper III indicating that survivors did not experience high annual expenses for dental treatment compared to references. Conversely, although the PC patients' DMFT is relatively similar to that of the elderly population of Norway, the mean number of decayed teeth was 1.85 (not reported in Paper II) and is four times higher than the mean number of decayed teeth (0.46) reported in elderly in Norway (203). Further, the prevalence of decayed teeth in elderly was reported to be 46% (203). These findings indicate that although approximately the same proportion of PC patients (51%) experience caries as elderly Norwegians, there is an increased number of decayed teeth per patient in this patient group. The survivors of ALL would have been 18 years around year 2000 AD based on the mean age at examination. At this time, the DMFT among 18-year-olds had stabilized around 5 (202). Applying a yearly increase of 0.15 DMFT per year they would have had an expected DMFT of approximately 6.7 at age 29, which is close to the 7.9 observed in our study, but much lower than the 9.6 recorded in the survivors diagnosed after the age of five years. These results indicate that it is important to inform patients about the increased risk of caries and implement a prophylactic regimen aimed at reducing caries development during and after cancer therapy in these patient groups.

There is considerable uncertainty regarding how to interpret the results reported above. Particularly that we do not have healthy, age and regionally matched reference groups that were examined clinically. Accordingly, the results regarding caries experience have to be compared to data available in the literature. Further, the study samples in both regional studies (North Trøndelag and Oslo) are representative for the populations of their particular geographic regions and accordingly include both healthy and sick participants. It has also been shown from national surveys that self-assessed oral health varies according to

geographic region in Norway (i.e. people in North Trøndelag assess their oral health as worse than people in the southeastern part of Norway) (144).

Comparison within study populations:

In the PC patients, no significant differences were found concerning caries experience or caries prevalence between patients who reported oral discomfort to those who did not (Paper II). This was an unexpected finding, but it may be because these patients received a high number of analgesics and antibiotics, have several other bothersome symptoms (i.e. xerostomia and taste alterations), or have a high tolerance for pain associated with caries. However, the DMFT and prevalence of caries observed in these patients are much higher than what has been reported for patients receiving chemotherapy (122). This was likely due to the high mean age of the study population, the advanced stage of disease, the high number of systemic drugs, and that there may have been a lack of systematic assessment and management of dental problems during current and previous treatments.

In accordance with other studies regarding long-term oral adverse effects in survivors of cancer during childhood and adolescence (139), we used age at diagnosis >/≤5 years as the grouping variable when comparing oral adverse effects within this patient population (Paper III). We found that receiving a diagnosis after the age of five years was significantly associated with a higher DMFT as adults compared to survivors who were younger when diagnosed (Paper III). This is similar to other studies reporting caries experience in long-term survivors after cancer during childhood and adolescence (139, 163). However, this does not exclude the possibility that patients who receive their diagnosis prior to the age of five also might have an increased amount of caries, as they would predominantly get caries in deciduous teeth. Hence, these teeth would be lost prior to the examination and not included in their caries experience as adults.

Gingivitis

Moderate to severe inflammation of the gingiva was a common finding across all three studies with a prevalence of 14 % among the outpatients and 11% among PC patients (Papers I-II). In paper III, the mean number of teeth with bleeding on probing was 18, with 69% having bleeding on probing around more than half of their remaining teeth (not reported in Paper III). Compared to the prevalence of severe gingivitis (approx. 20%, 95% confidence interval 0%-41%) in patients receiving chemotherapy reported in a MASCC / ISOO review (122), our results in the study populations in papers I and II are at the lower end of the confidence interval. The differences are likely due to differences between the study populations, diagnoses, or oral health regimens included in our studies and the studies included in the review. It may also be that the patients included in our studies have a good oral hygiene, or that the conditions around the clinical examinations might have contributed to an under-registration of gingivitis. However, severe gingivitis is defined as spontaneous bleeding in both indexes used in our studies (153, 154) and it is highly unlikely that this would have been missed. Another indication that the registrations were performed

adequately is that the gingivitis prevalence in paper III is similar to the global prevalence (50%-90%) presented in a recent Cochrane review (204). However, this finding also indicates that survivors of ALL during childhood and adolescence do not differ significantly from healthy individuals regarding periodontal health. Across all three studies (Papers I-III), gingivitis was present at a high rate, but was not significantly associated with any of the dependent variables (Papers I and II: oral discomfort; Paper III: age at diagnosis). However, it should be noted that gingivitis by nature weakens the tissue barrier and may act as a potential site of entry for bacteria and other pathogens in immunocompromised patients (122). In a MASCC / ISOO review, limited evidence from randomized controlled studies was found, and recommendations of specific oral hygiene measures during cancer therapy for cancers outside the head and neck area were not proposed (122). Nevertheless, the increased prevalence of caries and reduced gingival health found in such patients indicate that implementation of oral care regimens to prevent caries and periodontal disease, but also to prevent secondary infections and development of mucositis, may be important (90, 122).

Dental developmental defects

Dental developmental defects may negatively impact or complicate a survivor's future dental treatment needs (139, 164, 205). In paper III the prevalence and severity of certain dental developmental defects were reported in survivors of ALL during childhood and adolescence treated with chemotherapy. The prevalence of hypodontia in this study (5%) was similar to what was found in the Norwegian population (4.5%) (178). Microdontia (registered in 28% of the survivors), arrested root development (92% of the survivors had one or more teeth that deviated more than two standard deviations from the reference material), and enamel hypoplasia (registered in 46% of the survivors) were common in this study population. Further, our results showed an increased severity of dental defects (expressed through a higher IDeI-score) among survivors diagnosed at the age of 5 years or younger and those who received high doses of anthracyclines (anti-cancer antibiotics such as doxorubicin). Diagnosis ≤5 years was also significantly associated with a higher prevalence of enamel hypoplasia.

Individual Defect Index (IDeI)

Although we observed a higher severity of dental disturbances in survivors diagnosed ≤5 years of age compared to those who were older at diagnosis (IDeI-score: 18.0 vs. 9.6, $p<0.001$), both values are lower relative to other studies using different versions of this index (35, 158, 161). In a healthy study population from Finland, 89% had a IDeI score of 0 (maximum: 8) (158), whereas patients who had received HSCT with or without total body irradiation (TBI) had IDeI scores of 31.9 and 62.9 respectively (158). Further, they reported a significantly higher IDeI-score among survivors who were younger than five years when diagnosed compared to those who were older when diagnosed (158). Hsieh and co-workers (35) included several cancer diagnoses and treatment regimens in a study which evaluated dental developmental defects using Hölttä's original DeI (161). They found an average DeI

score of 24.7 and that the inclusion of a cyclophosphamide dose of >7500mg/m^2 induced an increase of approximately 13 defect points compared to patients who had not received cyclophosphamide. They did not observe similar results for other chemotherapeutic drugs. It should be noted that the DeI results in lower index scores than the IDeI due to different values assigned to the included defects (158). The most likely reason for these discrepancies is the inclusion of a high number of survivors who had received more aggressive treatment modalities (e.g. TBI and HSCT) in the other studies (35, 158). Other contributing factors may be the low number of missing teeth and the inclusion of only one diagnosis in our study. Our results indicated that high doses of anthracyclines (anti-cancer antibiotics) were associated with a higher severity of dental disturbances. Although alkylating agents (i.e. cyclophosphamide) and tubulin inhibitors (i.e. vincristine) were significantly associated with higher severity of dental developmental disturbances in the unadjusted models, they were not significant in the adjusted model. That high doses of anthracyclines are associated with development of dental aberrations adds to the knowledge concerning chemotherapeutic drugs associated with such defects in humans, as it has previously only been described in animal models (140, 206). This complements other studies that have found associations between increasing doses of cyclophosphamide or vincristine and dental developmental disturbances (35, 42, 43). In our study, the difference in IDeI score between those who had both associated factors (age at diagnosis ≤5 years and cumulative dose of anthracyclines >120mg/m^2) and those who were older and had received a lower dose were 21.4 IDeI-points. This signifies a difference of more than five microdontic teeth at the individual level between these two groups. Thus, it is paramount that information about such adverse effects is communicated to the caregivers (very young patients) prior to commencement of therapy.

Hypodontia

In a recent review, Gawade and co-workers reported that between 17% and 50% of survivors treated with chemotherapy for childhood cancers (ALL, lymphoma and neuroblastoma) had hypodontia (139). Hence, the prevalence of hypodontia in our study seems very low. When examining the articles included in the review, several explanations for this discrepancy are evident. For example, the study regarding ALL patients has an average examination age of 11.8 ±4.2 years and a prevalence of 50% (50). They reported that 19 of the 28 patients (68%) with hypodontia were treated with chemotherapy only and were below 5 years of age when treated (50). However, this study included 30 survivors who received chemotherapy only and no information was provided regarding inclusion of the wisdom teeth. If wisdom teeth were included in this material, the prevalence of hypodontia may be over-reported as the development of this tooth group is not discernable in a panoramic radiograph in many subjects at the age when these patients were examined (179). In a large self-report study which included over 9000 survivors of different childhood cancers and almost 3000 siblings showed a prevalence of approximately 8% of hypodontia among survivors vs. approximately 5% among siblings (42). However, only 25% of the participants in this study had received

chemotherapy only, and the prevalence among this group was not reported separately. They showed a dose-dependent risk of hypodontia and other dental developmental defects among survivors treated before the age of five who received alkylating agents (e.g. cyclophosphamide) (42). Given that the prevalence numbers reported from this study include a large proportion of survivors who had received other treatment modalities known to induce a higher prevalence of hypodontia (i.e. radiotherapy or chemoradiotherapy) (139), it is not unreasonable to assume that the prevalence among those who received chemotherapy were lower and comparable to our results. Our results does not indicate that chemotherapy is a risk factor for hypodontia in survivors of childhood ALL. However, the prevalence of hypodontia and number of missing teeth was very low in our study and the study sample may have been too small to show differences regarding this uncommon developmental defect.

Microdontia

Although microdontia is referred to as one of the most common dental developmental defects, its prevalence is only reported to be 2.2% and 1.6% in British school children and Turkish children respectively (205, 207). Hence, the prevalence of 28% reported from our study likely reflects an increased risk of this dental aberration associated with cancer treatment at a young age. Further, 29 (54%) of the survivors diagnosed ≤5 years and only 2 (4%) of those diagnosed at a higher age had microdontic teeth. These two were diagnosed at the age of five years and two weeks and 15 years respectively. Our findings are comparable to other studies with prevalence rates from 0% to 86% in survivors after different childhood cancers (45, 48, 50, 53, 161, 208). The discrepancy in prevalence rates is probably due to low numbers of participants that received chemotherapy only. One example is that in the study not reporting any microdontia only eight of 19 patients were treated before the age of five years (53). Another is the study with the highest registered prevalence rate of microdontia which only included eight patients (all received HSCT) who did not receive irradiation therapy and with seven of these receiving treatments before the age of five years (161). Our results show a clear association between chemotherapeutic treatment at a young age and microdontia. Hence, information about microdontia should be part of the routine information prior to treatment, including advice to close follow-up by the dentist, to evaluate potential needs for e.g. orthodontic treatment.

Arrested root development

Arrested root development was highly prevalent in our material and no significant difference was observed between age at diagnosis. Further, 71% of the patients had one or more teeth with an IDeI RC score of 2 or more, signifying a deviance of >3 SD from the reference teeth (not reported in Paper III). These findings are not unexpected as it likely reflects that teeth develop at different times and roots do not reach full length for some tooth groups before the age of 13 ±3 years (179). Hence, cancer therapy can induce root development aberrations within a much wider period than e.g. hypodontia and microdontia. Currently, there are not many studies which have addressed arrested tooth development in survivors

of childhood ALL. However, Sonis and co-workers recorded blunted or v-shaped roots in 13/19 (68%) survivors after childhood ALL who had not received irradiation therapy (53). Further, Hölttä reported that she found arrested root development (using the same method used in our study) in all survivors after HSCT (158). She did however note that the aberrations were less severe in patients who did not receive TBI (158). Few survivors in our material were treated with HSCT and none had received TBI, which may explain a lower prevalence relative to Hölttä. Caregivers and patients should be informed of this adverse effect as short roots may complicate e.g. orthodontic or periodontal treatment (139, 164).

Enamel hypoplasia

Enamel hypoplasia may predispose for caries (139, 164). Further, this may represent an esthetic problem due to visible defects and/or cause pain due to exposed dentin. In our study, 76% of the survivors diagnosed ≤5 years and 18% of those diagnosed when older had enamel hypoplasia. Similar results have been reported from other studies with prevalence rates ranging from 36% to 67% in different patient populations who did not receive cranial irradiation (50, 51, 209). However, it is of note that some studies have not found enamel hypoplasia in long-term survivors treated with chemotherapy (47, 53). It is unclear why the latter did not find any enamel hypoplasia in their materials when the former report a high prevalence. However, it is reasonable to assume that the method of registration differed between the studies and that few included survivors influenced the results (only 19 and 24 survivors included who had not received irradiation in the two studies that did not find such aberrations (47, 53)). Hence, it is important to advice patients and caregivers about the association between enamel hypoplasia and chemotherapy. An individual, prophylactic regimen with focus on tooth brushing, approximal hygiene and fluoride supplements are important to prevent and alleviate symptoms of enamel hypoplasia (139, 164). Further, therapy (conservative or prosthodontic) may be required in severe cases (139, 164).

Information regarding oral adverse effects

In both paper I and II few patients reported that they had received information about oral adverse effects of cancer and cancer therapy (27% and 22% respectively), measures to relieve xerostomia (30% and 38% respectively), or the importance of oral hygiene (27% and 31% respectively). However, the majority of patients in both studies were pleased with the information they had received (Paper I: 73%, Paper II: 81%). These results were surprising, as all patients had received a standardized information booklet at the start of treatment that included a segment concerning oral complications. This indicates that patients may not read and/or understand and/or retain written information provided to them, and that oral health care professionals should be included in oncology and PC teams to provide a continuous focus on oral health at all stages of the disease trajectory. Further, implementation of simple oral health assessment tools such as the EORTC QLQ-OH15 (181) in patient evaluation may increase the awareness about oral health issues among health care providers, identify patients who may need specialized oral care, and prevent more profound adverse effects.

Economic impact of long-term oral adverse effects

In paper III, economic impact of long-term oral adverse effects in survivors of ALL was investigated with out-of-pocket expenses within the previous year as the outcome variable. This was compared to age and regionally matched references. Despite our findings that demonstrated long-term oral adverse effects of chemotherapy in these survivors, they did not report higher out-of-pocket expenses than the references. Further, they did not visit the dentist more often or report poorer oral health compared to the references. To our knowledge, the long-term economic impact of oral adverse effects has not been addressed in other studies. However, several studies indicate that preventive measures before, during, and after treatment can help avoid future dental problems (42, 107, 210). This implies that there is a possible economic impact in the future if such measures are not implemented. However, we were not able to detect such an impact using the methods employed in this study. Another factor that may contribute to these findings is that survivors may have viewed defects at the levels recorded as minor and that they did not need treatment despite an objective need. Further, the survivors might not be informed and/or aware of their rights within the Norwegian health system, which could trigger at least partial reimbursement for some of their treatment needs, and therefore do not seek help.

CONCLUSIONS

According to the proposed aims, the studies included in this thesis showed that subjective and objective oral adverse effects are highly prevalent in cancer patients treated with chemotherapy for cancers outside the head and neck region in all phases of the disease trajectory. It also demonstrates that patients rarely remember information about oral adverse effects of therapy and oral care measures provided to them. Despite registering objectively assessed dental defects, we did not register a long-term economic impact of oral adverse effects in survivors of childhood ALL. The results from this thesis indicate that there is a need for a continuous focus on how to inform, diagnose, and manage oral cancer-related adverse effects at all stages of the disease trajectory, and that systematic collaboration with dental professionals may increase the detection of oral adverse effects at an early stage, thereby improving symptom management.

The conclusions from papers I-III are as follows:

Oral health and adverse effects:

- Xerostomia, mucositis and using a high number of concurrent drugs were significantly associated with oral discomfort in outpatients receiving chemotherapy for cancers outside of the head and neck area, whereas xerostomia and taste alterations were significantly associated with oral discomfort in PC patients.
- Among the outpatients and PC patients who reported oral discomfort, the highest mean scores indicating high symptom severity were found for xerostomia among the ten common cancer symptoms of the ESAS.
- Curative chemotherapy for childhood ALL results in long-term dental developmental defects, especially microdontia, disturbed root development, and enamel hypoplasia.
- Receiving a diagnosis before or at the age of five and cumulative doses of anthracyclines >120 mg/m^2 were strongly associated with increased severity of dental aberrations in survivors of ALL.
- Receiving a diagnosis after the age of five was associated with a higher caries experience in the permanent dentition in survivors of ALL.

Information:

- Few patients had retained information about oral complications or oral care measures provided to them in written form before treatment.

Economic impact:

- Adult survivors after childhood ALL reported lower annual expenses for dental treatment than matched references, albeit not significant among those who confirmed expenses within the past year.

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