

Cryoprevention of Chemotherapy-Induced Oral Mucositis

Aram Ibrahim

Department of Oral and Maxillofacial Surgery

Institute of Odontology

The Sahlgrenska Academy, University of Gothenburg, Sweden



UNIVERSITY OF GOTHENBURG

Gothenburg 2026

Cover illustration: Created using AI-assisted image generation and refined to align with the scientific theme of this thesis.

© Aram Ibrahim 2026
Aram.ibrahim@gu.se

ISBN 978-91-8115-639-3 (PRINT)
ISBN 978-91-8115-640-9 (PDF)
<http://hdl.handle.net/2077/90231>

Printed in Borås, Sweden 2026
Printed by Stema Specialtryck AB



*“Zimanê min
li rêyên dûr
li pey min tê
Ez wê winda nekir
ew li min re winda bû”*

*“My language
follows me
along distant roads
I did not lose it
it was lost with me”*

To my beloved family

Cryoprevention of Chemotherapy-Induced Oral Mucositis

Aram Ibrahim

Department of Oral and Maxillofacial Surgery, Institute of Odontology
The Sahlgrenska Academy, University of Gothenburg, Sweden

ABSTRACT

Oral mucositis (OM) is described as one of the most severe side effects of cancer therapy, causing immense pain that may significantly compromise treatment outcomes and increase healthcare costs. Cryoprevention using ice (IC) is a well-substantiated and recommended strategy for the prevention of chemotherapy-induced OM. However, the use of IC is associated with adverse reactions and infection risks from contaminated water. Evidence is also limited regarding optimal cooling temperature, timing and duration, leaving room for further optimization and increased tolerability of this modality. Furthermore, accurate diagnosis is essential for effective management of this condition.

The rationale for this thesis was to provide new insights into cryoprevention for chemotherapy-induced OM to improve the supportive care of cancer patients. The specific aims were to: *(i)* compare the ICD and IC in the prevention of OM (defined as peak OMAS-total) in a randomized controlled trial involving myeloma and lymphoma patients receiving high-dose chemotherapy in conjunction with hematopoietic stem cell transplantation; *(ii)* evaluate intraoral temperature reduction and tolerability using the ICD set to 8 °C and 15 °C, respectively, during 30 and 60 minutes of cooling; *(iii)* examine the trajectory of the intraoral temperature reduction using IC and ICD set to 8 °C and 15 °C, respectively, during a 30-minute cooling period; and *(iv)* evaluate interrater reliability between nurses and dentists specialized in orofacial medicine regarding OM assessments.

The ICD was equally effective as IC in preventing OM in myeloma patients, and even more effective in the lymphoma group (Study I). The ICD set to 15 °C was inferior to 8 °C in terms of reducing intraoral temperature (Study II). The greatest drop in intraoral temperature was seen after 5 minutes of cooling

with IC, the ICD set to 15 °C and 8 °C, respectively (Study III). For OM of any grade, the overall interrater reliability between nurses and dentists specialized in orofacial medicine was found to be fair (Study IV).

This thesis highlights that the ICD is promising in the prevention of OM and that cooling does not necessarily have to be prolonged or extremely cold to achieve clinical effect. This enables more individualized and tolerable cooling protocols. At the same time, the results highlight the need for increased knowledge, training and interprofessional collaboration in the diagnosis and management of OM.

Keywords: Cryotherapy, Intraoral cooling device, Oral mucositis, Multiple myeloma, Lymphoma, Hematopoietic stem cell transplantation, High-dose chemotherapy, Tolerability, Randomized controlled trial

ISBN 978-91-8115-639-3 (PRINT)

ISBN 978-91-8115-640-9 (PDF)

<http://hdl.handle.net/2077/90231>

SAMMANFATTNING PÅ SVENSKA

Oral mukositis (OM) beskrivs som en av de allvarligaste biverkningarna av cancerbehandling och orsakar smärta som avsevärt kan försämra behandlingsresultat och öka sjukvårdskostnader. Kryoprevention med is är en väl underbyggd och rekommenderad strategi för att förebygga kemoterapiinducerad OM. Användning av is är dock förknippad med biverkningar och infektionsrisker från förorenat vatten. Evidensen är också begränsad vad gäller när kylningen ska initieras, hur länge den ska fortgå efter avslutad cellgiftsinfusion samt vad som är den optimala intraoral kyltemperaturen. Detta lämnar utrymme för ytterligare optimering och ökad tolerans av denna metod. Dessutom är korrekt diagnostik avgörande för effektiv behandling av detta tillstånd.

Syftet med denna avhandling var att ge nya insikter i kryoprevention av kemoterapiinducerad OM för att förbättra cancervården. De specifika målen var att: (i) jämföra en intraoral kylanordning (ICD) och is för att förebygga kemoterapiinducerad OM i en randomiserad kontrollerad studie med myelom- och lymfompatienter som genomgår högdosbehandling med cellgifter i samband med stamcellstransplantation; (ii) utvärdera intraoral temperatursänkning och tolerabilitet med hjälp av ICD inställd på 8 °C och 15 °C under 30 och 60 minuters kylning; (iii) undersöka förloppet avseende intraoral temperatursänkning med is och ICD inställd på 8 °C respektive 15 °C under 30 minuters kylning; och (iv) utvärdera samstämmigheten mellan sjuksköterskor och tandläkare specialiserade inom orofacial medicin avseende OM-bedömningar.

ICD var lika effektiv som IC för att förebygga OM hos myelompatienter, och ännu mer effektiv i lymfomgruppen (Studie I). ICD inställd på 15 °C resulterade i lägre temperatursänkning i den intraoral slemhinnan jämfört med 8 °C (Studie II). Den största reduktionen i intraoral temperatur observerades efter 5 minuters kylning med is, ICD inställd på 8 °C och 15 °C (Studie III). Den övergripande samstämmigheten mellan sjuksköterskor och tandläkare specialiserade inom orofacial medicin befanns vara måttlig för OM av alla grader (Studie IV).

Denna avhandling belyser att ICD är lovande för att förebygga OM och att kryoprevention inte nödvändigtvis behöver vara långvarig eller extremt kall för att uppnå klinisk effekt. Detta möjliggör mer individualiserade och tolererbara kylprotokoll. Samtidigt belyser resultaten behovet av ökad kunskap, utbildning och tvärprofessionellt samarbete vid diagnos och behandling av OM.

LIST OF PAPERS

The author **Ibrahim A.** published earlier work under the name **Mahdi A.** Publications listed under **Ibrahim A.** and **Mahdi A.** refer to the same person.

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Walladbegi J., Henriksson R., Tavelin B., Svanberg A., Larfors G., Jadersten M., Schjesvold F., **Mahdi A.**, Garmin Legert K., Peterson E. D., Jontell M. Efficacy of a novel device for cryoprevention of oral mucositis: a randomized, blinded, multicenter, parallel group, phase 3 trial. *Bone Marrow Transplantation* 2022;57:191–7.
- II. **Mahdi A.**, Stubner J., Bergling M., Jontell J., Walladbegi J. Can cryoprevention of oral mucositis be obtained at a higher temperature? *Clinical Oral Investigations* 2021;25:4519–26.
- III. **Ibrahim A.**, Camci E., Khairallah L., Jontell M., Walladbegi J. Cryopreventive temperatures prior to chemotherapy. *Medical Oncology* 2023;40:1–7.
- IV. **Ibrahim A.**, Mahmoud D., Mavandadipur H., Walladbegi J. Interrater Reliability in the Assessment of Oral Mucositis among Patients Receiving High-Dose Chemotherapy: A Multicenter Comparison between Specialized Dentists and Registered Nurses. *BMC Cancer* 2025;25:1874–7.

All articles are reproduced with permission from the respective journals in accordance with the Creative Commons Attribution 4.0 International License (CC BY 4.0) (<http://creativecommons.org/licenses/by/4.0/>).

TABLE OF CONTENTS

| | |
|--|------|
| ABBREVIATIONS..... | xiii |
| 1 INTRODUCTION | 1 |
| 1.1 Background..... | 1 |
| 1.2 Cancer and treatment | 2 |
| 1.2.1 Multiple myeloma | 3 |
| 1.2.2 Lymphoma | 3 |
| 1.2.3 Chemotherapy | 4 |
| 1.2.4 High-dose chemotherapy | 4 |
| 1.2.5 Hematopoietic stem cell transplantation | 5 |
| 1.2.6 Autologous hematopoietic stem cell transplantation | 6 |
| 1.2.7 Allogenic hematopoietic stem cell transplantation | 6 |
| 1.2.8 Oral mucositis | 7 |
| 2 SCIENTIFIC QUESTIONS | 13 |
| 3 MATERIALS & METHODS | 15 |
| 3.1 Study designs | 15 |
| 3.2 Study population | 15 |
| 3.2.1 Study I and IV | 15 |
| 3.2.2 Study II and III..... | 15 |
| 3.3 Interventions and data collection | 16 |
| 3.3.1 Study I..... | 16 |
| 3.3.2 Study II..... | 17 |
| 3.3.3 Study III | 17 |
| 3.3.4 Study IV | 18 |
| 3.4 Outcome measures | 18 |
| 3.4.1 Study I..... | 18 |
| 3.4.2 Study II..... | 18 |
| 3.4.3 Study III | 18 |
| 3.4.4 Study IV | 19 |

| | | |
|-----|------------------------------|----|
| 3.5 | Statistical analyses | 19 |
| 3.6 | Ethical considerations | 20 |
| 4 | RESULTS | 21 |
| 4.1 | Study I..... | 21 |
| 4.2 | Study II | 22 |
| 4.3 | Study III..... | 23 |
| 4.4 | Study IV..... | 24 |
| 5 | DISCUSSION..... | 25 |
| 6 | CONCLUSION..... | 29 |
| 7 | FUTURE PERSPECTIVES..... | 31 |
| | ACKNOWLEDGEMENTS | 33 |
| | APPENDIX..... | 45 |
| | STUDIES I-IV | |

ABBREVIATIONS

| | |
|-------|--|
| AHSCT | Autologous hematopoietic stem cell transplantation |
| aHSCT | Allogenic hematopoietic stem cell transplantation |
| CMT | Chemotherapy |
| CT | Cryotherapy |
| G-CSF | Granulocyte colony-stimulating factor |
| GVHD | Graft-versus-host disease |
| GVT | Graft-versus-tumor |
| HDCT | High-dose chemotherapy |
| HLA | Human leukocyte antigen |
| HL | Hodgkin's lymphoma |
| HSCT | Hematopoietic stem cell transplantation |
| IC | Ice chips |
| ICD | Intraoral cooling device |
| ISOO | International Society of Oral Oncology |
| MASCC | Multinational Association of Supportive Care of Cancer |
| MM | Multiple myeloma |
| NHL | Non-Hodgkin's lymphoma |
| OMAS | Oral mucositis assessment scale |
| OM | Oral mucositis |
| PBM | Photobiomodulation |

| | |
|------|----------------------------|
| QoL | Quality of life |
| RT | Radiation therapy |
| SDCT | Standard-dose chemotherapy |
| WHO | World Health Organization |

1 INTRODUCTION

1.1 BACKGROUND

Oral mucositis (OM) is a common, painful, inflammatory condition of the mucous membranes lining the oral cavity and is described as one of the worst adverse effects of cancer therapy (Kanagalingam et al., 2018). OM is characterized by erythematous lesions, often combined with ulceration, resulting in substantial harm and burden for the patients and healthcare (Epstein and Miaskowski, 2019). Radiation therapy (RT) for head and neck malignancies and specific chemotherapy (CMT) regimens, particularly those used in preparation for high-dose chemotherapy (HDCT), e.g., for multiple myeloma and lymphoma, are well established etiological factors with high reported incidence (Elting et al., 2008, Elad et al., 2020).

Oral pain, dysphagia, the need for parenteral nutrition, extended hospitalization, and a reduced quality of life (QoL) are a few consequences of OM which potentially may interrupt cancer treatment, putting the patients in a life-threatening situation. Consequently, there is a pronounced clinical relevance to reduce the frequency of this adverse effect both to alleviate patient suffering and to decrease financial burden on the healthcare system that OM entails (Abdalla-Aslan et al., 2025). Therefore, the reliability and accuracy of OM diagnosis plays an important role and is a prerequisite for correct management and evaluation of different OM interventions. However, there is a lack of both knowledge regarding interrater variability, and consensus on which profession should have the primary responsibility regarding OM assessments among healthcare professionals. This may have a profound negative impact on the overall OM management.

The management of OM has undergone a shift from a palliative to preventive approach, driven by evidence that has accumulated over the past decades. Based on expert opinions by the Multinational Association of Supportive Care of Cancer/International Society of Oral Oncology (MASCC/ISOO), there are three recommended strategies for OM prevention (Elad et al., 2020). Cryotherapy (CT) using ice has been proven in several clinical trials to be the safest and most tolerable of these strategies (Correa et al., 2020). However, there remains a pronounced knowledge gap in the literature regarding critical aspects of CT that both impedes standardized protocols, and a wider implementation of this modality.

CT using ice is associated with considerable discomfort, such as chills, headache and shooting pain in the teeth (Walladbegi et al., 2017). More importantly, there is a potential health risk as ice made from contaminated water may expose immunocompromised patients to serious health risks (Kugler et al., 1983). To address these shortcomings and to understand the effect of CT on the intraoral tissues, a novel intraoral cooling device (ICD; Fig. 1) was developed.



Figure 1. The intraoral cooling device (ICD). Reprinted with permission from Walladbegi J., Gellerstedt M., Svanberg A., Jontell M. *Innovative intraoral cooling device better tolerated and equally effective as ice cooling.* *Cancer Chemother Pharmacol.* 2017 Nov; 80(5):965-72. (<http://creativecommons.org/licenses/by/4.0/>).

1.2 CANCER AND TREATMENT

Cancer is the second leading cause of mortality worldwide, following cardiovascular diseases, and accounted for an estimated 9.7 million deaths in 2022 (Bray et al., 2024). Globally, data from the World Health Organization (WHO) reveal that 1 in 6 (~ 17 %) deaths are due to cancer (WHO, 2020). In Sweden, approximately 60 thousand cases of cancer are diagnosed every year, with an even distribution between the sexes. However, despite being a prosperous country of high-quality healthcare with advanced diagnostic tools and well-established treatment strategies, the number of new cases has increased by an average of 1.7 % per year over the last 20 years. The most common cancers are solid, including prostate and breast followed by skin, colorectal and lung cancer, which together account for ~ 50 % of the cases. The corresponding figures for non-solid, hematological malignancies, multiple

myeloma (MM), various forms of lymphoma and acute and chronic leukemias constitute ~ 7 % (4800 cases) of the annual diagnoses in Sweden. These diagnoses and their corresponding treatment strategies are frequently associated with the development of OM and are therefore of interest to highlight in this thesis (Cancerfonden, 2024c).

1.2.1 MULTIPLE MYELOMA

MM is a clonal plasma cell (activated B-lymphocytes) malignancy in the bone marrow characterized by an abnormal production of monoclonal paraproteins, predominantly immunoglobulin G and A. In the bone marrow, the neoplasm affects the hematopoiesis which results in several symptoms including anemia, leukopenia, osteoclast-mediated bone destruction and hypercalcemia (Nau and Lewis, 2008).

In 2022, MM accounted for ~ 188 thousand new cases worldwide and resulted in more than 120 thousand deaths (Mafra et al., 2025). According to data from the Swedish cancer registry, MM constitutes approximately 660 new cases/year in Sweden. The disease is unusual before 60 years of age and is more common among men than women. The course of illness differs between individuals and the prognosis is significantly correlated with age. The 10-year survival after diagnosis is 37 % (Cancerfonden, 2024b). However, despite improvement in previously poor survival rates, MM is considered incurable (Bergsagel, 2014).

1.2.2 LYMPHOMA

Lymphoid neoplasms are divided into two main subgroups, Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL), which in turn comprise approximately 30 distinct subtypes (Aisenberg, 2000, Cancerfonden, 2023). The diverse forms of lymphoma present with widely varying clinical- and histopathological features and differ in terms of prognosis.

Lymphoma is the most common hematological neoplasm in industrialized countries and, as a group, ranks as the seventh most common cancer in adults and the third most common in children (Kaatsch, 2010, Huh, 2012, McGuire, 2016). Lymphomas accounted for ~ 3.5 % of all global malignancies and for ~ 300 thousand deaths worldwide in 2022 (Bray et al., 2024). In Sweden approximately 2500 cases are registered every year. NHL is the dominant subgroup and represents ~ 2000 of the cases. NHL is further categorized in low- and high malignant lymphoma where the low malignant form is characterized by a slow progression with few or no symptoms at all. On the

contrary, the high malignant form has a more dramatic course and may present with certain non-specific symptoms including weight loss, fatigue and prolonged or recurrent fever without signs of infection, as well as low survival rates. Lymphoma may affect everyone but is more common among men than women and is unusual before 60 years of age. Most lymphomas arise in B-lymphocytes, but about 10 % are T-cell associated and occur more frequently among young individuals (Matasar and Zelenetz, 2008, Cancerfonden, 2024a).

The prognosis differs significantly, depending on the type and stage of lymphoma, but is generally better for low-grade lymphomas. The 5- and 10-year relative survival rates are 75 % and 60-65 % respectively (Cancerfonden, 2024a).

1.2.3 CHEMOTHERAPY

Chemotherapeutic drugs are a class of agents with systemic effects, meaning that they can target tumors at any anatomic location. The cytotoxic effects of CMT induce cell-cycle arrest and lead cells to undergo apoptosis, generally by inhibiting microtubule function, protein function, or DNA synthesis. The underlying mechanisms vary and may be cell cycle-dependent or cell cycle-independent, primarily affecting tumor cell proliferation or directly damaging DNA, respectively. Cytotoxic drugs are generally categorized as alkylating agents, antimetabolites, antitumor antibiotics, topoisomerase inhibitors, and mitotic inhibitors. However, there are certain agents that act via alternative mechanisms and cannot be classified in any of the aforementioned categories.

Cancer cells may vary widely in their susceptibility to CMT, hence sometimes combined or used in conjunction with other cancer modalities (Shewach and Kuchta, 2009). Furthermore, cytotoxic agents lack selectivity and may in addition to cancer cells, target rapidly proliferating healthy cells, thereby increasing the risk of adverse effects, including OM.

Standard-dose chemotherapy (SDCT) regimens have proven effective for many cancers (Imrie et al., 2002). However, they are insufficient to cure certain malignancies, such as MM, relapsed lymphoma, and acute leukemias. In these settings, high-dose chemotherapy (HDCT) (myeloablative conditioning) has emerged as an effective approach.

1.2.4 HIGH-DOSE CHEMOTHERAPY

HDCT refers to CMT regimens administered at higher doses than SDCT and is sometimes combined with local or total body irradiation due to its ability to penetrate sanctuary sites. HDCT eradicates cancerous cells and induces

immunosuppression to facilitate engraftment of stem cells as part of myeloablative conditioning, consequently reducing the risk of potential graft rejection (Locatelli et al., 2014, Bacigalupo et al., 2009).

The rationale for HDCT is that many anti-cancer agents exhibit a steep dose-response relationship, i.e., small increases in dosage result in large increases in cancer cell destruction (Porrata and Adjei, 2001). However, although cancer cells are killed to a greater extent, higher doses of cytotoxic agents often result in an increased severity and incidence of CMT-induced morbidity (e.g., infections, hemorrhage and organ failure). While SDCT causes transient bone marrow suppression, myeloablative conditioning is more hazardous and results in prolonged marrow aplasia, a potentially life-threatening state that requires hematopoietic stem cell support for recovery (Rodriguez et al., 2007). This procedure, hematopoietic stem cell transplantation (HSCT), is prepared in advance by harvesting and cryopreserving stem cells prior to conditioning therapy. Stem cells are collected from bone marrow or umbilical cord blood, or most commonly from peripheral blood. (Felfly and Haddad, 2014, Park et al., 2015).

1.2.5 HEMATOPOIETIC STEM CELL TRANSPLANTATION

HSCT is a procedure in which the bone marrow is replaced due to infections, disease or conditioning myeloablative therapy. Treatment outcomes were initially poor but development of methods, which allowed for donor and recipient HLA matching, eventually led to one of the greatest medical successes in history (Moore and Sakamoto, 2005, Henig and Zuckerman, 2014). In Sweden, the first HSCT was performed in 1975 at the Karolinska University Hospital, Huddinge.

In theory, HSCT following myeloablative conditioning versus conventional SDCT alone has two major advantages. Firstly, it allows higher doses of cytotoxic agents compared to standard-dose which would otherwise be toxic to the bone marrow. Secondly, depending on the type of transplantation (i.e. autologous or allogenic) graft-versus-tumor (GVT) effect may positively affect the cancer treatment outcomes (Moore and Sakamoto, 2005, Porter, 2011).

In the current era, HDCT followed by HSCT is the standard of care for several malignant conditions (e.g. MM and lymphoma) as well as selected non-malignant disorders. HSCT is categorized as autologous (AHSCT) or allogenic (aHSCT). The type of malignancy, sensitivity to CMT, availability of a suitable

donor, patient age, and susceptibility of the malignancy to GVT effects influence the suitability of each treatment modality (Majhail et al., 2015). An estimated 93 thousand HSCT were performed worldwide in 2018. Of these ~ 49 thousand are AHSCT and ~ 44 thousand aHSCT (Atsuta et al., 2024). The estimated yearly figures in Sweden are 600 AHSCT and 400 aHSCT.

1.2.6 AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Prior to AHSCT, a careful examination of the cardiovascular function, comorbidity and performance status is performed to ensure that the patient is suitable for treatment. The process that follows comprises administration of bone marrow stimulating drugs, granulocyte colony-stimulating factor (G-CSF), extraction of stem cells (apheresis) and storage of harvested cells in a freezer. Subsequent procedures include myeloablative therapy, with HDCT and/or RT, and transfusion of the patient's own stored stem cells. Thus, AHSCT is not a true "transplant" in this context. Later, within 2-3 weeks, the infused stem cells replace the damaged tissue and start to restore the patient's hematopoiesis (Ali et al., 2015).

AHSCT is associated with a low overall risk of infection due to rapid immune reconstitution and with a low incidence of transplant rejection and graft-versus-host disease (GVHD), since donor and recipient are the same individual. However, the early post-transplant period remains critical, as patients face their greatest risk of infection and post-transplant mortality (Shlomchik, 2007).

1.2.7 ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Allogenic hematopoietic stem cell transplantation (aHSCT) is different from AHSCT and involves two individuals: the transplant donor and the recipient who are matched with a human leukocyte antigen (HLA), a protein which is expressed in duplicate on the cell surface and is considered of great importance to the immune system. The donor, who can be related or unrelated, and the recipient should preferably have identical HLA-matched stem cells, to reduce the risk of transplant rejection and GVHD. Approximately 30 % of aHSCT recipients have a fully HLA-matched donor, and even these patients may suffer from GVHD due to mismatches in minor histocompatibility antigens (Hansen et al., 1980, Singh and McGuirk, 2016).

Cancer therapy, particularly HDCT followed by HSCT, is a complex and resource-intensive process associated with multiple potential adverse effects. Although the risk of developing adverse effects varies among patients, mucositis and more specifically OM, along with its associated symptoms are frequently reported in the literature (Epstein et al., 2012, Migliorati et al., 2015, Berger et al., 2018).

1.2.8 ORAL MUCOSITIS

OM comes with a significant burden for patients with pronounced negative impact on treatment outcome and economic consequences for the healthcare (Vera-Llonch et al., 2007, Elting and Chang, 2019). The incidence varies depending on the treatment regimen, with SDCT being associated with an incidence of around 40 %, whereas OM is observed in up to 80 % among patients receiving HDCT (Berger et al., 2018). RT-regimens are even more tissue damaging with reported incidences of up to 100 % (Berger et al., 2018).

1.2.8.1 PATHOBIOLOGY

The cytotoxic effect of CT induces a complicated, preclinical cascade of inflammatory events in the subepithelium that precedes the clinical manifestation of OM. This has been described in a 5-stage process: 1) initiation; 2) primary damage response; 3) signal amplification; 4) ulceration; and 5) healing. In general, the cytotoxic agent induces tissue damage that consequently results in the activation of transcription factors, pro-inflammatory cytokines such as interleukin-6 and TNF-alpha, and reactive oxygen species, which mainly drive the inflammatory response subsequently resulting in tissue damage (Fig. 2) (Bowen et al., 2019).

1.2.8.2 CLINICAL CHARACTERISTICS

Clinically, patients receiving CMT typically experience a sore and stinging sensation in the oral mucosa a few days following infusion. Symptoms develop gradually and generally peak in intensity around days 10-14 until it spontaneously resolves after 2-4 weeks (Sonis, 2009). The course of OM in patients receiving RT therapy is more pronounced and prolonged, with ulcerations remaining up to 4 weeks following the last dose of radiation (Sonis, 2009). The presence of secondary infection may prolong the duration of OM, further compromising nutrition and increasing the risk for systemic infections.

1.2.8.3 DIAGNOSIS

Severe grades of OM (Fig. 2) not only necessitate parenteral analgesic intervention, but also affect cancer treatment through dose limitations and, in

some cases, treatment interruption (Elting et al., 2003). The extensive negative impact of OM inevitably places high demands on accurate diagnosis and management. The diagnosis of OM typically relies on clinical examination of the oral mucosa in combination with patient-reported symptoms, reflecting both objective and subjective clinical findings. Several validated instruments are described in the literature for the assessment and grading of OM severity, of which the World Health Organization toxicity scale (WHO-scale) and Oral Mucositis Assessment Scale (OMAS) are two of the most commonly used (Sonis et al., 1999). The latter, however, does not consider patient-reported symptoms.

There is currently no consensus on which healthcare profession should hold the primary clinical responsibility for OM assessments. In Scandinavian countries, daily assessments are usually conducted by nurses and occasionally by dentists specialized in orofacial medicine throughout the course of treatment. Consequently, there is considerable heterogeneity in assessment practices in hospitals and across countries. Studies comparing reliability and accuracy in OM assessments between different professions are lacking which potentially jeopardize patient safety and the interpretation of previous studies in the field of OM. On the other hand, several studies highlight an inadequate knowledge regarding the oral cavity and its diseases among nurses (Raymond and Agyeman-Yeboah, 2023, Gundogdu and Sayar, 2022). Furthermore, no evidence-based guidelines exist regarding which clinical healthcare profession should be responsible for the OM assessments.

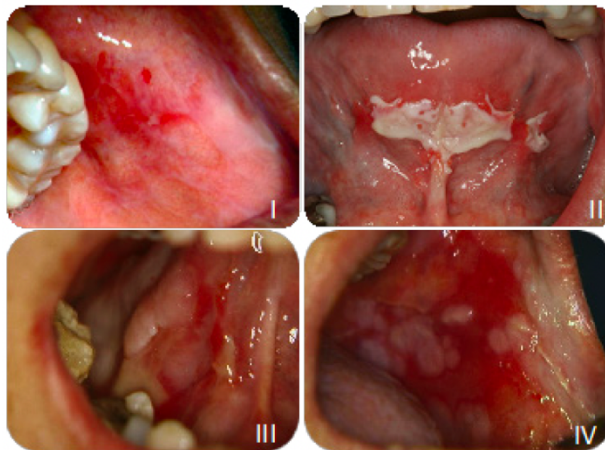


Figure 2. Oral mucositis, Grades I–IV (World Health Organization scale). Grades III and IV are considered as severe oral mucositis. Photographs courtesy of Dr. D. Öhman, The Sahlgrenska Academy, University of Gothenburg, Sweden.

1.2.8.4 PREVENTION

Over the past decades, various strategies have been introduced to treat already established OM. However, due to varying clinical outcomes, inconsistent evidence and the complex pathobiology of OM, interventions have shifted from treatment to prevention. Three preventive interventions are recommended by the MASCC/ISOO: *Recombinant human keratinocyte growth factor-1 (Palifermin)*, *photobiomodulation (PBM)* and *oral cryotherapy* (Elad et al., 2020).

Recombinant human keratinocyte growth factor-1 (Palifermin)

The general principle behind growth factors is the stimulation of cell growth, proliferation and differentiation. By affecting structural components in the oral mucosa, such as epithelial cells, fibroblasts and keratinocytes, Palifermin strengthens the integrity of the intraoral mucosa making it more resistant to OM and interacts with several pathways that mediate the inflammatory response. However, the administration of Palifermin is based on intravenous injections several days before, and after HDCT, and comes with a considerable cost exceeding 8000 USD per patient. Further, significant side effects have been reported, such as taste alterations, paresthesia and pruritus (Radtko and Kolesar, 2005). Hence, Palifermin has been withdrawn from the European Medicines Agency since 2006.

Photobiomodulation (PBM)

PBM is based on non-ionizing light around 650nm, with pain relieving, anti-inflammatory and wound healing properties (Courtois et al., 2021). PBM is a well-studied intervention both for prevention and treatment of established OM. The MASCC/ISOO recommends the use of PBM in prevention of OM for patients treated with HDCT in conjunction with HSCT with or without total body irradiation, and for patients receiving RT or RT-CT for head and neck cancer. However, PBM is linked to concerns. The large number of different PBM devices on the market has complicated the development of standardized protocols. Chair time, lack of training, cost of the PBM-device and concerns about malignant transformation are factors reported by clinicians, limiting the adoption of this intervention (Courtois et al., 2021, Abdalla-Aslan et al., 2023).

Cryotherapy

CT is one of the most substantiated interventions in the prevention of OM and is recommended for patients receiving HDCT in conjunction with AHSCT or SDCT with bolus 5-fluorouracil (Elad et al., 2020). The generally accepted theory is that temperature reduction in the oral mucosa results in local vasoconstriction, thus reducing the amount of the cytotoxic chemotherapeutic agent reaching the tissue. In addition, colder temperatures may reduce the cellular metabolism in the oral epithelium, which could further limit the cytotoxic impact of CMT in the oral mucosa (Walladbegi et al., 2023).

In recent decades, several studies have shown promising results mainly using ice chips (IC), for the prevention of CMT-induced OM (Correa et al., 2020). Unfortunately, the use of CT has not lived up to its preventive potential, which may be attributed to several reasons.

1.2.8.5 LIMITATIONS OF CRYOTHERAPY USING IC

Despite the promising preventive effect of CT using IC, this modality comes with several aspects that must be considered. The use of IC has been reported to induce headache, tooth sensations and chills, all of which may affect patient compliance and tolerability (Kadokia et al., 2014). Further, current evidence shows varying cooling protocols, i.e. when cooling should be commenced, for how long, and at which cooling temperature. This may be attributed to the lack of knowledge with respect to the optimal temperature for OM prevention. More importantly, severe grades of OM disrupt the integrity of the intraoral mucosa exposing the immunocompromised patient to a higher risk of infection (Jensen and Peterson, 2014, Riley et al., 2015). This places high demands on the quality of water used in the production of IC to avoid microbial contamination.

Taken together, these factors may be the reason for the limited use of CT using IC in the prevention of OM worldwide.

1.2.8.6 THE INTRAORAL COOLING DEVICE

The limitations of IC have consequently resulted in a need for innovation in the field of CT (Kadokia et al., 2014). To overcome the obstacles that exist with IC and enable an increased clinical implementation, the ICD was developed (Fig. 1).

The ICD is a portable cooling and thermostat unit. It consists of conduits for circulating water with an adjustable temperature between 6 °C and 22 °C at a

flow rate of 0.25 L/min. The soft-plastic design comes at different sizes and cools the cheeks, lips, floor of the mouth, tongue, gums and hard palate.

1.2.8.7 TIMING AND TEMPERATURE

Given the theory of vasoconstriction and reduced cell metabolism, it is believed that the lowest achievable temperature in the oral mucosa provides the best conditions for OM prevention. Intraoral cooling is initiated prior to CMT infusion, continues during, and for some time after infusion. While the post-infusion cooling is dependent on the half-life of the chemotherapeutic drug, pre-infusion cooling time is not standardized. The lack of evidence on when the lowest temperature is achieved during cooling probably explains the variations, from minutes to hours, seen in cooling protocols in the literature.

Regardless of cooling temperature, an intraoral temperature plateau seems to occur following 5 minutes of cooling (Study III). There is also evidence suggesting that a moderate reduction in intraoral temperature of just a few degrees Celsius may be sufficient to prevent OM (Walladbegi et al., 2023). This knowledge questions whether longer cooling sessions are needed for OM prevention.

2 SCIENTIFIC QUESTIONS

The overall goal of this thesis was to increase the understanding of cryoprevention of OM. The specific aims of this thesis, which were defined to answer the scientific questions, were as follows: *(i)* to compare the ICD and IC in the prevention of OM (defined as peak OMAS-total) in a randomized controlled trial involving myeloma and lymphoma patients receiving HDCT in conjunction with HSCT; *(ii)* evaluate intraoral temperature reduction and tolerability using the ICD set to 8 °C and 15 °C, respectively, during 30 and 60 minutes of cooling; *(iii)* examine the trajectory of the intraoral temperature reduction using IC and ICD set to 8 °C and 15 °C, respectively, during a 30-minute cooling period; *(iv)* evaluate interrater reliability between nurses and dentists specialized in orofacial medicine regarding OM assessments.

Scientific questions:

1. Is there a difference in peak OMAS-total between myeloma- and lymphoma patients using the ICD and IC, during HDCT in conjunction with HSCT? (Study I)
2. Is there a difference in intraoral temperature reduction when cooling with the ICD set to 8 °C and 15 °C? (Study II)
3. Is cooling better tolerated with the ICD set to 15 °C compared to 8 °C? (Study II)
4. When is the steady state temperature in the intraoral mucosa achieved when cooling with IC, and the ICD set to 8 °C and 15 °C, respectively? (Study III)
5. Is the assessment of OM severity comparable between dentists specialized in orofacial medicine and registered nurses? (Study IV)

3 MATERIALS & METHODS

3.1 STUDY DESIGNS

Study I was a randomized controlled clinical trial and included patients diagnosed with myeloma and lymphoma scheduled for HDCT followed by HSCT to evaluate the effect of the ICD in preventing OM. Given the results of Study I, Study II was designed as a crossover trial in healthy volunteers to assess the cooling efficacy of higher cooling temperatures (8- and 15 °C) than used previously. A crossover design on healthy volunteers was also conducted in Study III, where the intraoral temperatures during a clinically relevant time of cooling were analyzed using different cooling temperatures. Study IV was a retrospective, secondary analysis of data obtained from Study I regarding OM assessments between specialized dentists and nurses.

3.2 STUDY POPULATION

3.2.1 STUDY I AND IV

Study I and IV consisted of 182 eligible patients recruited between June 2017 and November 2019. The study was conducted at five university hospitals in Sweden and Norway: Uppsala University Hospital, Karolinska University Hospital, Linköping University Hospital, Örebro University Hospital, and Oslo University Hospital. The participants had confirmed multiple myeloma (n=156; 85.7 %) or lymphoma (n=26; 14.3 %), were ≥ 18 years of age, and scheduled for HDCT and HSCT treatment. Furthermore, eligible patients had to be suitable candidates for high-dose regimen with melphalan (for multiple myeloma) or BEAC/BEAM (for lymphoma), as assessed by the investigator. The BEAC regimen included carmustine, cytarabine, etoposide, and cyclophosphamide, whereas cyclophosphamide was replaced by melphalan in the BEAM regimen.

3.2.2 STUDY II AND III

Study II and Study III each included 20 healthy dental students and were conducted in 2018 and 2021, respectively. Study II comprised 5 men and 15 women with a mean age of 23 years (SD \pm 1 year). The corresponding figures for Study III were 10 men and 10 women and a mean age of 27 years (SD \pm 3 years). Both studies were carried out at the Department of Oral Medicine and

Pathology, Institute of Odontology, The Sahlgrenska Academy, University of Gothenburg, Sweden. Eligibility criteria were based on the following: no medical diagnoses established by physician; no medication with any impact on the cardiovascular system and no use of tobacco or oral tobacco products or snuff.

3.3 INTERVENTIONS AND DATA COLLECTION

CT was a recurring intervention across the studies in this thesis. Different cooling methods and protocols were used and evaluated as potential procedures to prevent OM. Conventional CT using IC and the ICD set at 8- and 15 °C were used. All studies in this thesis shared the same basic cooling concept, however, they differed in design and approach and included not only physiological outcomes of CT, but also and clinical and diagnostic aspects of OM.

3.3.1 STUDY I

Patients diagnosed with myeloma or lymphoma were randomized (1:1) to intraoral cooling with either IC or the ICD. The cooling session continued for 1.5 h for myeloma patients. Patients diagnosed with lymphoma and scheduled for BEAC regimen were subjected to 1.5-3.5 h cooling sessions, 1-2 times a day for 5 consecutive days. The cooling protocol for lymphoma patients scheduled for the BEAM regimen was 1-2h cooling sessions, 1-2 times per day for 6 consecutive days. For all patients, cooling was initiated 30 minutes prior to CMT infusion, maintained throughout infusion, and continued for 30 minutes post-infusion.

IC was made from tap water with an approximate temperature of -0.5 °C upon cooling. The ICD was available in 2 sizes (medium and large) and set to 8 °C (± 2 °C). Prior to each cooling session, patients received instructions on how to cool the intraoral mucosa using IC and the ICD.

OM was assessed by clinical examination using OMAS (Oral Mucositis Assessment Scale) by dentists specialized in oral medicine, three times a week until discharge or until day +28 after HSCT. Areas of assessment included buccal and palatal mucosae, lips, floor of the mouth, tongue, and gingiva. Intraclass correlation (ICC) was calculated to measure the interrater agreement between the dental staff. To assess tolerability, patients completed a

questionnaire describing perceived pain in association with the cooling procedure. Patients were also asked to fill out a validated QoL instrument (the functional assessment of cancer therapy – general; FACT-G) at admission and at discharge.

The questionnaires used in Study I are published in full together with the original article and are therefore not reproduced in the appendix of this thesis.

3.3.2 STUDY II

In this experimental, double-blinded crossover study healthy volunteers were randomized to cool the intraoral mucosa using the ICD set at 8- or 15 °C. Each participant attended two cooling sessions with at least 24 hrs between sessions.

A thermographic camera (FLIR E60 (bx), FLIR Systems Inc., Wilsonville, OR, USA) was used to record intraoral temperatures at baseline, following 30- and 60 minutes, respectively. All recordings were conducted by the same two investigators, who had previously undergone calibration to ensure standardization. The intraoral sites of interest were buccal and palatal mucosae, lips, floor of the mouth, tongue, and gingiva. The mean intraoral temperature for each site was calculated using the FLIR software tool. Following each of the two cooling sessions, participants were asked to fill out a questionnaire related to tolerability and adverse events. After completing both cooling sessions, each participant was asked which of the two sessions they preferred.

3.3.3 STUDY III

Healthy volunteers were randomized to three intraoral cooling sessions in a crossover design, using IC and the ICD set at 8- and 15 °C, respectively. To prevent carry-over effects, a minimum washout period of 24 hrs was implemented between each session. Each cooling session lasted 30 minutes, during which intraoral temperature was recorded using a thermographic camera (FLIR E60 (bx), FLIR Systems Inc., Wilsonville, OR, USA) at baseline and following 5, 10, 15, 20, and 30 minutes. Measurements were taken at the following intraoral sites: buccal and palatal mucosae, lips, floor of the mouth, tongue, and gingiva. Consistent with the methodology in Study II, the mean intraoral temperature for each site was calculated by two blinded investigators using the FLIR software tool.

3.3.4 STUDY IV

No intervention was carried out in Study IV, which was a secondary analysis of data collected from Study I. This study compared OM assessments between dentists specialized in orofacial medicine and registered nurses, using the WHO-scale.

3.4 OUTCOME MEASURES

In this thesis, the outcomes were primarily related to degree of OM developed in cancer patients treated with HDCT followed by HSCT, effect and tolerability of CT using different cooling protocols, and diagnostic variability between specialized dentists and nurses.

3.4.1 STUDY I

The primary endpoint was the highest OMAS score recorded (peak-OMAS) in myeloma and lymphoma patients using IC or the ICD. The secondary endpoints concerned tolerability and oral pain perceived in association with the intraoral cooling using IC and the ICD. Following each cooling session, patients were instructed to fill out a study specific questionnaire measuring tolerability and a numeric pain rating scale (NPRS) to assess oral pain (defined as NPRS \geq 3). Numerous tertiary variables were gathered by nurses and can be found in the published paper.

3.4.2 STUDY II

To understand the efficacy of shorter cooling durations and higher cooling temperatures than used in Study I, this study focused on the difference in mean temperature reduction using the ICD applying different protocols. For this purpose, healthy volunteers were randomized to intraoral cooling with the ICD set to 8- and 15 °C for 60- and 30 minutes, respectively.

3.4.3 STUDY III

The dynamics of the intraoral mucosa during a course of 30 minutes of cooling was analyzed in Study III. The main aim of this study was to measure the intraoral temperature following 5, 10, 15, 20- and 30 minutes of cooling to assess when along the cooling period a steady state temperature is achieved applying different cooling protocols.

3.4.4 STUDY IV

To measure reliability and accuracy of OM assessments between dentists specialized in orofacial medicine and registered nurses, a comparison of OM scores based on the WHO-scale was performed.

3.5 STATISTICAL ANALYSES

A multiple linear regression model was used to analyze the primary endpoint in Study I. Differences in mean peak OMAS-total between the treatment groups were tested with the Mann-Whitney U-test. The probability of free peak OMAS-total ≥ 3 for the two intervention groups, considering each diagnosis separately, were estimated using the Kaplan-Meier method and the log-rank test. Primary and safety analyses were performed by intention-to-treat. The statistical analyses were employed using the IBM SPSS Statistics software package (IBM SPSS Statistics version 25, IBM, Armonk, NY). A p-value ≤ 0.05 was considered statistically significant.

In Study II, differences in mean temperature reduction ($^{\circ}\text{C}$) after 60 minutes and 30 minutes of cooling between the ICD set to 8°C and 15°C , were analyzed using a mixed model ANOVA. The difference in mean temperature reduction ($^{\circ}\text{C}$) between 30 and 60 minutes of cooling with the ICD set to 8°C and 15°C , respectively, were analyzed in the same manner. Tolerability, expressed by “Which of the two cooling sessions did you tolerate better?”, was calculated with a McNemar test and adverse events were presented descriptively. A p-value ≤ 0.05 was considered statistically significant and calculations were performed using the IBM SPSS Statistics software package (IBM SPSS Statistics version 25, IBM, Armonk, NY).

Normality assumption in Study III was controlled using the Shapiro-Wilk and a Gaussian distribution was confirmed for all the tested variables. To determine any statistically significant differences in temperature reduction after 5 minutes of cooling between IC, and $\text{ICD}^{8^{\circ}\text{C}}$ or $\text{ICD}^{15^{\circ}\text{C}}$, One-way analysis of variance (ANOVA) was performed, followed by a post hoc test, Tukey, for multiple comparisons. A two-sided paired samples Student’s t-test was performed to assess any statistical differences between 5 and 30 minutes of cooling within each cooling method. A p-value ≤ 0.05 was considered statistically significant.

The calculations were performed using the IBM SPSS Statistics software package (IBM SPSS Statistics version 24, IBM, Armonk, NY).

To evaluate the interrater reliability in Study IV, Cohen's Kappa (κ) statistics was used. Wilcoxon signed-rank test was used to determine statistically significant differences between OM severity ratings provided by the orofacial medicine specialist and the nurse for each specific assessment. A p -value of ≤ 0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS Statistics software package, version 26 (IBM Corp., Armonk, NY, USA).

3.6 ETHICAL CONSIDERATIONS

For Study I and Study IV, ethical approval was obtained by the Swedish Ethical Review Authority, Sweden (Reference number 586-15), and the Regional Committee for Medical and Health Research Ethics, Oslo, Norway (Reference number 2018/1653).

Study II was performed in accordance with the ethical principles established in the WMA Declaration of Helsinki (Fortaleza, October 2013). The study was also reviewed and approved by the Department of Oral Medicine and Pathology, Institute of Odontology, The Sahlgrenska Academy, University of Gothenburg, Sweden, which was a request by the regional ethical review board in Gothenburg. The regional ethical review board in Gothenburg itself did not consider an ethical application necessary.

Study III was reviewed and approved by the Swedish Ethical Review Authority (Reference No. 2021-01020).

4 RESULTS

4.1 STUDY I

OM of any grade was found in 44.2 % (76/172) of the entire cohort of this study whereas severe OM, defined as $OMAS \geq 3$, was diagnosed in 19.3 % (33/172) of the patients. When comparing IC and the ICD in the prevention of OM in the whole study population, no statistically significant difference was found ($\bar{x} \pm SD$; 1.24 ± 1.61 vs. 0.99 ± 1.47 ; $p=0.351$) (Fig. 3). Further analysis of the preventive effect of IC and the ICD revealed no differences within the myeloma group ($\bar{x} \pm SD$; 0.92 ± 1.41 vs. 0.85 ± 1.41 ; $p=0.734$). However, when analyzing the lymphoma group, a statistically significant difference was observed between the IC and the ICD ($\bar{x} \pm SD$; 3.08 ± 1.50 vs. 1.77 ± 1.59 ; $p=0.047$) (Fig. 3).

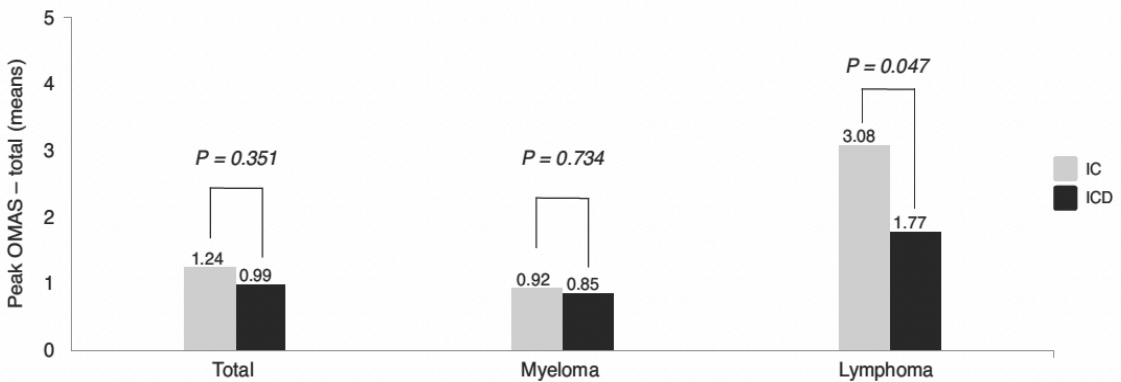


Figure 3. Peak OMAS-total (mean) for the total population, myeloma group, and the lymphoma group following cooling with ice chips (IC) or the intraoral cooling device (ICD).

4.2 STUDY II

Cooling for 60 minutes using the ICD set to 8 °C resulted in a mean intraoral temperature reduction of 7.69 °C. The corresponding figure when the ICD was set to 15 °C was 5.21 °C. The difference of 2.48 °C was statistically significant ($p < 0.001$; 95 % CI 1.30 to 3.40) (Fig. 4).

A mean intraoral temperature reduction of 6.89 °C and 5.02 °C was observed following 30 minutes of cooling when the ICD was set to 8 °C and 15 °C, respectively. The difference of 1.87 °C between the cooling temperatures was statistically significant ($p < 0.001$; 95 % CI 0.73 to 2.60) (Fig. 4). However, when compared to how much further an additional 30 minutes of cooling reduced the intraoral temperature at 8 °C and 15 °C, respectively, no statistically significant differences were found.

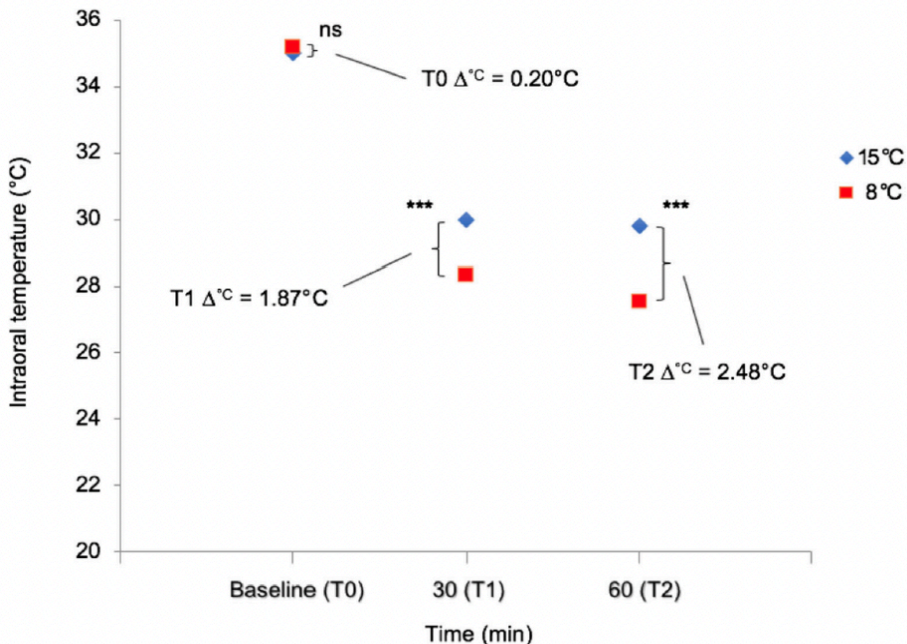


Figure 4. Comparison between intraoral temperatures at baseline (T0), 30 minutes (T1) and 60 minutes (T2), with the intraoral cooling device (ICD) set to 8 °C and 15 °C, respectively; ns, not significant; *** $p < 0.001$.

The questionnaire addressing tolerability was completed by all subjects and revealed that 75 % (15/20) preferred cooling with the ICD set to 15 °C ($p < 0.001$; 95 % CI 50.9 to 91.3).

4.3 STUDY III

The greatest drop in mean intraoral temperature was seen following 5 minutes of cooling for all cooling temperatures, i.e., IC and ICD set to 8 °C or 15 °C (Fig. 5). Compared to baseline, IC resulted in a temperature reduction of 6.2 °C whereas the corresponding figures for the ICD set to 8 °C or 15 °C were 5.5 °C and 4.5 °C, respectively.

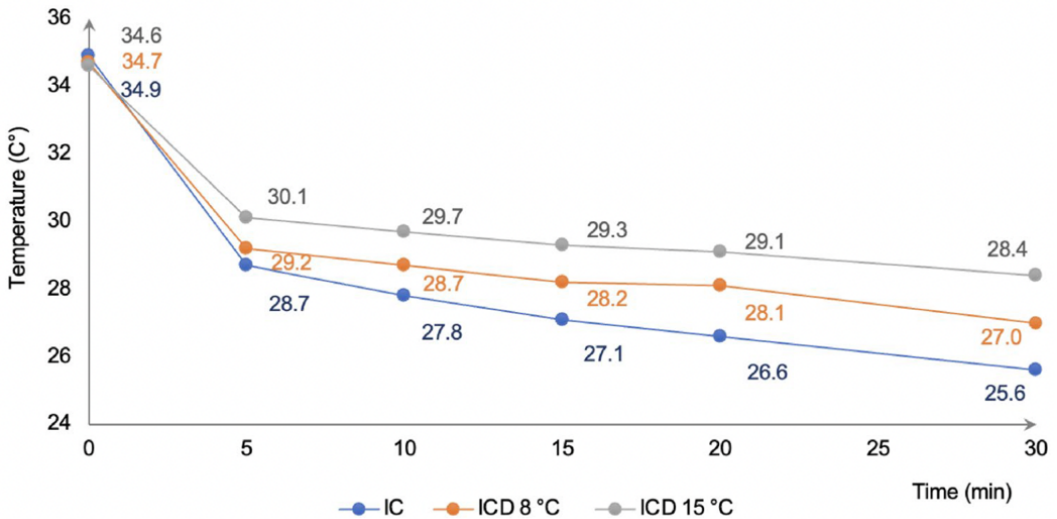


Figure 5. Intraoral mucosal temperatures at baseline and following 5, 10, 15, 20, and 30 minutes of cooling with ice chips (IC), and the intraoral cooling device (ICD) set to 8 and 15 °C, respectively.

When comparing the intraoral temperature at 5 and 30 minutes, an additional temperature decrease of 3.1 °C for IC, 2.2 °C for ICD set to 8 °C and 1.7 °C for ICD set to 15 °C was observed (Fig. 6). The difference was statistically significant for all three methods ($p < 0.001$).

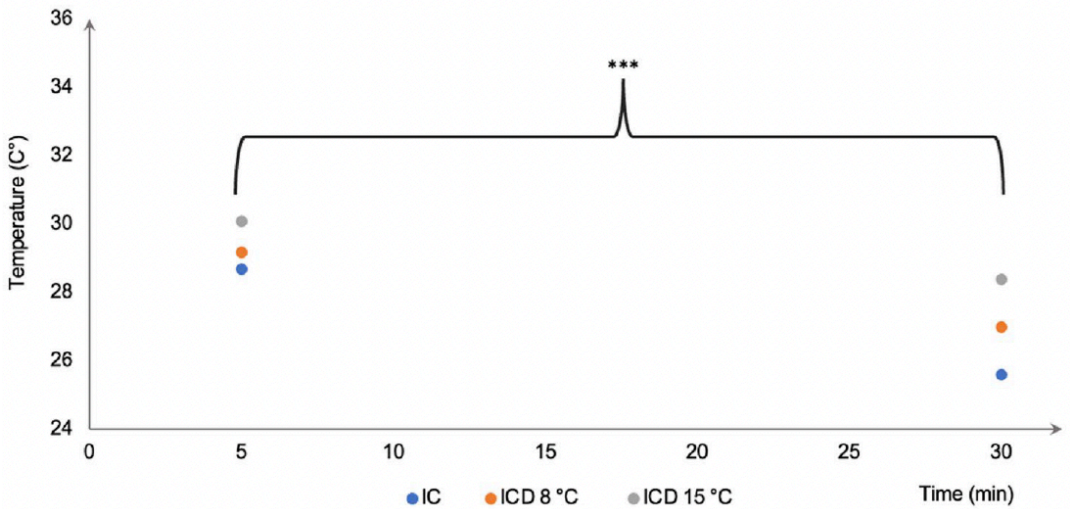


Figure 6. Intraoral mucosal temperatures at baseline and following 5, 10, 15, 20, and 30 minutes of cooling with ice chips (IC), and the intraoral cooling device (ICD) set to 8 and 15 °C, respectively. *** $p < 0.001$.

4.4 STUDY IV

In total, 127 OM assessments using the WHO-scale were conducted by dentists specialized in orofacial medicine and registered nurses. The results showed that severe OM was associated with lower interrater reliability between the professions regarding OM assessments. Grade 0 showed an interrater agreement of 63 % (41/65). The agreement for severe OM (grade 3 and 4), corresponded to 1/9 (11 %) and 0/2 (0 %), respectively.

5 DISCUSSION

OM is an often neglected but potentially deadly side effect of HDCT in conjunction with autologous HSCT. OM results in increased risk for infections, complicating nutrition and cancer treatment, and reduces QoL for affected patients (Epstein and Miaskowski, 2019, Lalla et al., 2019, Barkokebas et al., 2015). The serious outcome of OM is not only a burden for the patients as it also comes with considerable resource utilization, particularly for cases of severe OM with incremental cost for OM-hospitalization estimated up to 375,000 USD (Elting and Chang, 2019). Despite evidence confirming the preventive efficacy of cryoprevention in this matter, the implementation of this method is limited. In this context, a novel ICD was developed as an alternative to traditional IC to improve efficacy, tolerability and to reduce the potential risk of infection that is associated with IC made of contaminated water for this specific group of patients (Walladbegi et al., 2017).

The results from the studies in this thesis collectively indicate that the ICD is at least as effective as IC in the prevention of OM, with a superior safety profile as the risk of infection from contaminated water is eliminated. Furthermore, the ICD showed increased tolerability especially when using higher cooling temperatures (Study I and Study II). The improved tolerability may be crucial in increasing patient compliance with cryoprevention, which in turn may positively impact adherence to cancer treatment. The ICD was also shown in Study I to be particularly effective and tolerable for lymphoma patients, who are subjected to extensive chemotherapeutic protocols with longer cooling sessions compared to patients diagnosed with myeloma. For the myeloma group, the ICD was equivalent to IC in preventing OM. Thus, the efficacy of the ICD in the prevention of OM was clearly demonstrated. As Study I was not primarily designed to compare tolerability of the two cooling modalities, any conclusion regarding this manner is primarily based on previous studies on healthy volunteers. However, difficulty swallowing reported by participants randomized to the ICD suggests that patient compliance could be improved by enhancing tolerability through technical modifications of the ICD, such as size optimization. Another limitation was the small number of lymphoma patients, which were enrolled from one study site and subjected to BEAC, with less pronounced OM compared to BEAM (Jantunen et al., 2003).

The results from Study I raised the question whether higher cooling temperatures may increase tolerability further without compromising OM

prevention. Therefore, in Study II the difference in mean intraoral temperature reduction between intraoral cooling using ICD^{8°C} and ICD^{15°C} for 30- and 60 minutes was analyzed. Although the observed difference of approximately 2 °C was statistically significant, the clinical relevance remains questionable. Study II showed that the greatest drop in intraoral temperature occurs during the first 30 minutes of cooling when a steady state temperature is achieved, thus questioning the benefit of longer cooling sessions. It is well substantiated that cooling using colder temperatures is associated with several adverse events, such as cold, headache and teeth sensations (Walladbegi et al., 2017). This was confirmed in Study II where higher cooling temperatures seemed to further increase tolerability, as ICD^{15°C} was preferred by the majority of participants. Considering the delicate structure of the intraoral mucosa, it appears reasonable that higher cooling temperatures are sufficient to achieve adequate temperature reduction locally in the mucosal tissue for OM prevention (Qin et al., 2017, Prestin et al., 2012). This is further indicated in an animal model where cooling temperature of 30 °C may be sufficient to affect the early inflammatory processes that precede clinically manifest OM (Walladbegi et al., 2023). This challenges the theory that the coldest temperature is also the most effective in preventing OM.

Another important aspect of cryoprevention is when the cooling should be commenced in relation to CMT infusion. For all cooling methods used in Study III (IC, ICD^{8°C} and ICD^{15°C}) the greatest drop in intraoral temperature was observed following the initial 5 minutes of cooling. The intraoral temperature continued to decrease, however, to a limited degree for the remaining 25 minutes of cooling. Consequently, the pattern observed indicates that the therapeutic effect may be achieved early in the cooling procedure. This observation is confirmed in several clinical studies where cooling is commenced 5-10 minutes prior to CMT infusion with low incidence of severe OM reported (Askarifar et al., 2016, Batlle et al., 2014, Rocke et al., 1993). This further indicates that even moderate intraoral temperature reduction may be enough to prevent the early inflammatory processes that precede OM.

These findings may have important clinical implications as shorter cooling sessions may improve tolerability and potentially make cryoprevention feasible for a wider range of clinical situations. Defining the optimal cooling protocol (i.e., when cooling should be commenced and its duration) was an aspect that motivated the need to understand when, during the 30-minute cooling period, steady-state temperature is achieved.

An interesting finding of this thesis, demonstrated in Study IV, was only moderate intergroup agreement between the two professions regarding OM assessment. This raises questions about diagnostic reliability in healthcare. Although from a resource and cost perspective it is not always realistic to involve specialist dentists in every OM assessment, the importance of strengthening nurses' competence through education and further training is emphasized. A possible solution is the integration of specialized dentists as permanent members of multidisciplinary teams in hematology and oncology settings. This can lead to more consistent assessments, earlier interventions and improved patient outcomes, ultimately reducing the need for more expensive OM-associated complications, such as extended hospitalization. An additional interesting finding from Study IV was that interrater reliability varied between different study centers and that it declined as OM severity increased. An aspect to consider when interpreting the results is that statistical significance was not reached, although a trend was observed. An explanation for this may be that the entire study population received cryotherapy, which is an effective preventive intervention. Thus, the lower number of cases of severe OM in this study may have masked the differences in diagnostic reliability between the professions. However, the observed pattern demonstrated in this study emphasizes the importance of standardized assessment tools and protocols for OM grading. It is also conceivable that the varying level of education and experience of the nurses played a role, where previous research has shown that only half received formal training in OM and only 10 % received more than five hours of training in the area (Gundogdu and Sayar, 2022).

From a healthcare perspective, cost-effectiveness should also be considered. OM is not only associated with increased patient suffering but also with extended care times, need for parenteral nutrition and intravenously administered opioids for pain relief (Epstein and Miaskowski, 2019, Lalla et al., 2019). Even if an investment in cooling systems and training of personnel initially entails a cost, in the longer term this can reduce the use of resources in health care and thus be both economically and ethically justifiable.

Despite the promising results, the studies have also identified limitations. For example, the lymphoma cohort in Study I was small and recruited from one study center, limiting generalizability. The thermographic camera for temperature measurement in Study II and Study III in the oral cavity was not originally intended for intraoral measurements, which may affect the accuracy of the data. However, the same method was used for all comparisons, which likely minimizes systematic errors within each study.

6 CONCLUSION

This thesis highlights that the ICD is promising in the prevention of OM, with documented efficacy, improved comfort and increased safety in environments where water supply and quality may be uncertain. Furthermore, cooling does not necessarily have to be prolonged or extremely cold to achieve clinical effect, which enables more individualized and tolerable cooling protocols. At the same time, the results highlight the need for increased knowledge, training and interprofessional collaboration in the diagnosis and management of OM.

To further develop the field of cryoprevention, future studies in a broader range of cancer diagnoses are needed, including subgroups at higher risk of developing OM within general oncology. Furthermore, patients with head and neck cancers receiving radiation therapy are particularly vulnerable to OM. However, the potential risk of protecting malignant cells using cryotherapy must be investigated. Improved tolerability by technical improvements of the ICD is needed and implementation of standardized assessment methods as well as clearer protocols for start time, duration and temperature during intraoral cooling should also be prioritized. With these measures, OM prevention can take a significant step forward, both scientifically and clinically.

7 FUTURE PERSPECTIVES

Several interesting questions for future research were raised during this thesis. First, the accumulating evidence supporting the use of higher cooling temperatures prompts the question of how much further the temperature can be increased without compromising prevention OM. Given the delicate structure of the intraoral mucosa, only a modest reduction in temperature may be required. In fact, findings from animal models incubated at 30 °C have demonstrated beneficial effects on early inflammatory processes in the intraoral mucosa that precede clinically manifest OM (Walladbegi et al., 2023).

Second, the question arises whether extraoral cooling could achieve an effect equivalent to intraoral cooling in the prevention of OM. In a feasibility study involving non-cancer patients, this approach resulted in a reduction of intraoral temperatures by 2-3 °C (Najaf et al., 2023). Such modality has the potential to overcome several limitations associated with of the ICD and intraoral cooling in general, including reported discomfort and challenges related to device sizing, cooling sensations, and headache, thereby further improving tolerability and patient compliance. Moreover, extraoral cooling may facilitate wider implementation of CT, for example in pediatric populations. It may also expand the anatomical reach of CT to include additional sites at risk, such as the oro- and hypopharynx/esophagus.

Ultimately, the emergence of modern cancer treatments, such as targeted- and immune therapies, have been associated with novel oral mucosal toxicities and oral mucosal immune-related adverse events. The clinical manifestation and underlying pathobiology of these conditions have not been studied in depth but likely differ from OM associated with conventional cancer treatment, rendering this an interesting area for future research.

ACKNOWLEDGEMENTS

Supervisors

Main supervisor, Dr Java Walladbegi, from our very first conversation in the university cafeteria many years ago, I recognized how much we had in common. Our love for FC Barcelona and the tiki-taka philosophy, we had similar football injuries that ended up hindering our football careers, and a shared passion that reached beyond the boundaries of dentistry. Most importantly, we shared the same Kurdish background and culture. Our parents endured persecution and oppression and escaped, risking their lives for our future. Our shared interests and the philosophy we have in common have taken us on a beautiful journey together. I still smile when I think about how long we walked to find the best döner kebab in Marseille during the EBMT conference back in 2017. This is one of the many unforgettable memories we created along the way. You have always emphasized the importance of setting an example to inspire the younger generation, especially children from our background, to give them motivation and hope, and to show that nothing is impossible. This philosophy to give back to society has shaped how I will approach everything I encounter in the future. I will be forever grateful that you took me under your wings and believed in me, from my very first moments at the emergency dental clinic on weekends to this special day. You have not only been my supervisor, but also a friend, brother, role model and mentor in life.

Co-supervisor, Professor Mats Jontell, thank you for your unwavering support throughout these years. You have been my role model since I started dental school and a true inspiration. Your dignity and immense experience have always fascinated me, and I am incredibly proud to share this journey with you. From the bottom of my heart, I am grateful for your guidance and scientific support.

Co-supervisor, Professor Lars Rasmusson, I am sincerely grateful for giving me the opportunity to this research project at your department and for your guidance and support throughout the years. You have been a true inspiration for me.

Colleagues

I want to express my sincere gratitude to the **Sahlgrenska Academy** and **Department of Oral and Maxillofacial Surgery** at the **University of Gothenburg** for these years.

To all the staff at **Braincool AB**, thank you for your trust in me and giving me the opportunity to be a part of one of the biggest projects in the world within our field.

Svea Partners AB, thank you for your support during this Ph.D. Without you **Abbas**, this wouldn't be possible.

Anncarin Svanberg, we had a great time together traveling to all the university hospitals during the research project. Thank you for your support and always staying positive.

To all the staff I had the privilege to work with at **Uppsala University Hospital, Karolinska University Hospital, Linköping University Hospital, Örebro University Hospital, and Oslo University Hospital**. Thank you for always welcoming me and making my work easier.

Family

Mum and **dad**, you escaped evil and took us to paradise. Your childhood was sacrificed but you gave us life and hope. My love for you is endless. You taught me the true meaning of life and family.

My beloved wife **Roxana**. I'm so grateful that I didn't drop out from dental school because that's where I fell in love with you. My dear, I appreciate all the days and hours you stood up for me. You make my life beautiful. **Tiago** and **Ronia**, my beautiful children, dad loves you so much and you are the true meaning of my life.

My dear brothers, **Haval** and **Ramiar**, I can't describe how proud I am of you. I believe in you and your potential. Never be afraid of your dreams, follow them. **Olivia**, you are so smart and sweet and a future Ph.D will be an easy task for you. Your presence in my life gives me energy and hope and I can't wait for what the future holds. Your support and love are invaluable. I love you.

Lina Najaf, thank you for not only being my dear cousin, but also like a sister to me. Your endless support, and the way you always checked up on me and my research, have meant a lot. Thank you for always being there when I needed you. I am truly grateful.

The Ghafori brothers, **Hadi, Abbas, and Ali**. I want to express my gratitude for your support and belief. Thank you for always encouraging the best in others and for always being there when it mattered. I am truly grateful to have such beautiful souls in my life.

REFERENCES

- ABDALLA-ASLAN, R., KEEGAN, R., ZADIK, Y., YAROM, N. & ELAD, S. 2025. Recent advances in cancer therapy-associated oral mucositis. *Oral Dis*, 31, 2695–710.
- ABDALLA-ASLAN, R., ZADIK, Y., INTRATOR, O., BARDELLINI, E., CHENG, K. K. F., BOSSI, P., YAROM, N. & ELAD, S. 2023. Clinical use of photobiomodulation for the prevention and treatment of oral mucositis: the real-life experience of MASCC/ISOO members. *Support Care Cancer*, 31, 481–91.
- AISENBERG, A. C. 2000. Historical review of lymphomas. *Br J Haematol*, 109, 466–76.
- ALI, N., ADIL, S. N. & SHAIKH, M. U. 2015. Autologous Hematopoietic Stem Cell Transplantation-10 Years of Data From a Developing Country. *Stem Cells Transl Med*, 4, 873–7.
- ASKARIFAR, M., LAKDIZAJI, S., RAMZI, M., RAHMANI, A. & JABBARZADEH, F. 2016. The Effects of Oral Cryotherapy on Chemotherapy-Induced Oral Mucositis in Patients Undergoing Autologous Transplantation of Blood Stem Cells: A Clinical Trial. *Iran Red Crescent Med J*, 18, e24775.
- ATSUTA, Y., BALDOMERO, H., NEUMANN, D., SUREDA, A., DEVOS, J. D., IIDA, M., KARDUSS, A., PURTILL, D., ELHADDAD, A. M., BAZUAYE, N. G., BONFIM, C., DE LA CAMARA, R., CHAUDHRI, N. A., CICERI, F., CORREA, C., FRUTOS, C., GALEANO, S., GARDERET, L., GONZALEZ-RAMELLA, O., GRECO, R., HAMAD, N., HAZENBERG, M. D., HOROWITZ, M. M., KALWAK, K., KO, B. S., KODERA, Y., KOH, M. B., LIU, K., MCLORNAN, D. P., MOON, J. H., NEVEN, B., OKAMOTO, S., PASQUINI, M. C., PASSWEG, J. R., PAULSON, K., RONDELLI, D., RUGGERI, A., SEBER, A., SNOWDEN, J. A., SRIVASTAVA, A., SZER, J., WEISDORF, D., WOREL, N., GREINIX, H., SABER, W., ALJURF, M. & NIEDERWIESER, D. 2024. Continuous and differential improvement in worldwide access to hematopoietic cell transplantation: activity has doubled in a decade with a notable increase in unrelated and non-identical related donors. *Haematologica*, 109, 3282–94.

- BACIGALUPO, A., BALLEEN, K., RIZZO, D., GIRALT, S., LAZARUS, H., HO, V., APPERLEY, J., SLAVIN, S., PASQUINI, M., SANDMAIER, B. M., BARRETT, J., BLAISE, D., LOWSKI, R. & HOROWITZ, M. 2009. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*, 15, 1628–33.
- BARKOKEBAS, A., SILVA, I. H., DE ANDRADE, S. C., CARVALHO, A. A., GUEIROS, L. A., PAIVA, S. M. & LEAO, J. C. 2015. Impact of oral mucositis on oral-health-related quality of life of patients diagnosed with cancer. *J Oral Pathol Med*, 44, 746–51.
- BATLLE, M., MORGADES, M., VIVES, S., FERRA, C., ORIOL, A., SANCHO, J. M., XICOY, B., MORENO, M., MAGALLON, L. & RIBERA, J. M. 2014. Usefulness and safety of oral cryotherapy in the prevention of oral mucositis after conditioning regimens with high-dose melphalan for autologous stem cell transplantation for lymphoma and myeloma. *Eur J Haematol*, 93, 487–91.
- BERGER, K., SCHOPOHL, D., BOLLIG, A., STROBACH, D., RIEGER, C., RUBLEE, D. & OSTERMANN, H. 2018. Burden of Oral Mucositis: A Systematic Review and Implications for Future Research. *Oncol Res Treat*, 41, 399–405.
- BERGSAGEL, P. L. 2014. Where we were, where we are, where we are going: progress in multiple myeloma. *Am Soc Clin Oncol Educ Book*, 199–203.
- BOWEN, J., AL-DASOOQI, N., BOSSI, P., WARDILL, H., VAN SEBILLE, Y., AL-AZRI, A., BATEMAN, E., CORREA, M. E., RABER-DURLACHER, J., KANDWAL, A., MAYO, B., NAIR, R. G., STRINGER, A., TEN BOHMER, K., THORPE, D., LALLA, R. V., SONIS, S., CHENG, K., ELAD, S. & MUCOSITIS STUDY GROUP OF THE MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER/INTERNATIONAL SOCIETY OF ORAL, O. 2019. The pathogenesis of mucositis: updated perspectives and emerging targets. *Support Care Cancer*, 27, 4023–33.
- BRAY, F., LAVERSANNE, M., SUNG, H., FERLAY, J., SIEGEL, R. L., SOERJOMATARAM, I. & JEMAL, A. 2024. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 74, 229–63.

-
- CANCERFONDEN. 2023. *Cancer i siffror* [Online].
<https://www.cancerfonden.se/cancer-i-siffror>
[Accessed: 27 December 2025].
- CANCERFONDEN. 2024a. *Lymfom* [Online].
<https://www.cancerfonden.se/om-cancer/cancersjukdomar/lymfom>
[Accessed 27 December 2025].
- CANCERFONDEN. 2024b. *Statistik myelom* [Online].
<https://www.cancerfonden.se/om-cancer/statistik/myelom>
[Accessed 27 December 2025].
- CANCERFONDEN. 2024c. *Statistik om cancer* [Online].
<https://www.cancerfonden.se/om-cancer/statistik>.
[Accessed 27 December 2025].
- CORREA, M. E. P., CHENG, K. K. F., CHIANG, K., KANDWAL, A., LOPRINZI, C. L., MORI, T., POTTING, C., ROULEAU, T., TORO, J. J., RANNA, V., VADDI, A., PETERSON, D. E., BOSSI, P., LALLA, R. V. & ELAD, S. 2020. Systematic review of oral cryotherapy for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer*, 28, 2449–56.
- COURTOIS, E., BOULEFTOUR, W., GUY, J. B., LOUATI, S., BENSADOUN, R. J., RODRIGUEZ-LAFRASSE, C. & MAGNE, N. 2021. Mechanisms of PhotoBioModulation (PBM) focused on oral mucositis prevention and treatment: a scoping review. *BMC Oral Health*, 21, 220–31.
- ELAD, S., CHENG, K. K. F., LALLA, R. V., YAROM, N., HONG, C., LOGAN, R. M., BOWEN, J., GIBSON, R., SAUNDERS, D. P., ZADIK, Y., ARIYAWARDANA, A., CORREA, M. E., RANNA, V., BOSSI, P., MUCOSITIS GUIDELINES LEADERSHIP GROUP OF THE MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN, C. & INTERNATIONAL SOCIETY OF ORAL, O. 2020. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*, 126, 4423–31.
- ELTING, L. S. & CHANG, Y. C. 2019. Costs of Oral Complications of Cancer Therapies: Estimates and a Blueprint for Future Study. *J Natl Cancer Inst Monogr*, 2019, 116–23.
-

- ELTING, L. S., COOKSLEY, C., CHAMBERS, M., CANTOR, S. B., MANZULLO, E. & RUBENSTEIN, E. B. 2003. The burdens of cancer therapy. Clinical and economic outcomes of chemotherapy-induced mucositis. *Cancer*, 98, 1531–9.
- ELTING, L. S., KEEFE, D. M., SONIS, S. T., GARDEN, A. S., SPIJKERVET, F. K., BARASCH, A., TISHLER, R. B., CANTY, T. P., KUDRIMOTI, M. K., VERA-LLONCH, M., BURDEN OF ILLNESS, H. & NECK WRITING, C. 2008. Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life. *Cancer*, 113, 2704–13.
- EPSTEIN, J. B. & MIASKOWSKI, C. 2019. Oral Pain in the Cancer Patient. *J Natl Cancer Inst Monogr*, 2019, 45–53.
- EPSTEIN, J. B., THARIAT, J., BENSADOUN, R. J., BARASCH, A., MURPHY, B. A., KOLNICK, L., POPPLEWELL, L. & MAGHAMI, E. 2012. Oral complications of cancer and cancer therapy: from cancer treatment to survivorship. *CA Cancer J Clin*, 62, 400–22.
- FELFLY, H. & HADDAD, G. G. 2014. Hematopoietic stem cells: potential new applications for translational medicine. *J Stem Cells*, 9, 163–97.
- GUNDOGDU, F. & SAYAR, S. 2022. Oncology nursing practices in the management of chemotherapy-related oral mucositis in accordance with evidence-based guidelines: a descriptive and cross-sectional study. *Support Care Cancer*, 30, 9549–57.
- HANSEN, J. A., CLIFT, R. A., THOMAS, E. D., BUCKNER, C. D., STORB, R. & GIBLETT, E. R. 1980. Transplantation of marrow from an unrelated donor to a patient with acute leukemia. *N Engl J Med*, 303, 565–7.
- HENIG, I. & ZUCKERMAN, T. 2014. Hematopoietic stem cell transplantation-50 years of evolution and future perspectives. *Rambam Maimonides Med J*, 5, e0028.
- HUH, J. 2012. Epidemiologic overview of malignant lymphoma. *Korean J Hematol*, 47, 92–104.

-
- IMRIE, K., ESMAIL, R., MEYER, R. M. & MEMBERS OF THE HEMATOLOGY DISEASE SITE GROUP OF THE CANCER CARE ONTARIO PRACTICE GUIDELINES, I. 2002. The role of high-dose chemotherapy and stem-cell transplantation in patients with multiple myeloma: a practice guideline of the Cancer Care Ontario Practice Guidelines Initiative. *Ann Intern Med*, 136, 619–29.
- JANTUNEN, E., KUITTINEN, T. & NOUSIAINEN, T. 2003. BEAC or BEAM for high-dose therapy in patients with non-Hodgkin's lymphoma? A single centre analysis on toxicity and efficacy. *Leuk Lymphoma*, 44, 1151–8.
- JENSEN, S. B. & PETERSON, D. E. 2014. Oral mucosal injury caused by cancer therapies: current management and new frontiers in research. *J Oral Pathol Med*, 43, 81–90.
- KAATSCH, P. 2010. Epidemiology of childhood cancer. *Cancer Treat Rev*, 36, 277–85.
- KADAKIA, K. C., ROZELL, S. A., BUTALA, A. A. & LOPRINZI, C. L. 2014. Supportive cryotherapy: a review from head to toe. *J Pain Symptom Manage*, 47, 1100–15.
- KANAGALINGAM, J., WAHID, M. I. A., LIN, J. C., CUPINO, N. A., LIU, E., KANG, J. H., BAZARBASHI, S., BENDER MOREIRA, N., ARUMUGAM, H., MUELLER, S. & MOON, H. 2018. Patient and oncologist perceptions regarding symptoms and impact on quality-of-life of oral mucositis in cancer treatment: results from the Awareness Drives Oral Mucositis PercepTion (ADOPT) study. *Support Care Cancer*, 26, 2191–200.
- KUGLER, J. W., ARMITAGE, J. O., HELMS, C. M., KLASSEN, L. W., GOEKEN, N. E., AHMANN, G. B., GINGRICH, R. D., JOHNSON, W. & GILCHRIST, M. J. 1983. Nosocomial Legionnaires' disease. Occurrence in recipients of bone marrow transplants. *Am J Med*, 74, 281–8.
- LALLA, R. V., BRENNAN, M. T., GORDON, S. M., SONIS, S. T., ROSENTHAL, D. I. & KEEFE, D. M. 2019. Oral Mucositis Due to High-Dose Chemotherapy and/or Head and Neck Radiation Therapy. *J Natl Cancer Inst Monogr*, 2019, 17–24.
-

- LOCATELLI, F., LUCARELLI, B. & MERLI, P. 2014. Current and future approaches to treat graft failure after allogeneic hematopoietic stem cell transplantation. *Expert Opin Pharmacother*, 15, 23–36.
- MAFRA, A., LAVERSANNE, M., MARCOS-GRAGERA, R., CHAVES, H. V. S., MCSHANE, C., BRAY, F. & ZNAOR, A. 2025. The global multiple myeloma incidence and mortality burden in 2022 and predictions for 2045. *J Natl Cancer Inst*, 117, 907–14.
- MAJHAIL, N. S., FARNIA, S. H., CARPENTER, P. A., CHAMPLIN, R. E., CRAWFORD, S., MARKS, D. I., OMEL, J. L., ORCHARD, P. J., PALMER, J., SABER, W., SAVANI, B. N., VEYS, P. A., BREDESON, C. N., GIRALT, S. A. & LEMAISTRE, C. F. 2015. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*, 21, 1863–69.
- MATASAR, M. J. & ZELENETZ, A. D. 2008. Overview of lymphoma diagnosis and management. *Radiol Clin North Am*, 46, 175–98.
- MCGUIRE, S. 2016. World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015. *Adv Nutr*, 7, 418–9.
- MIGLIORATI, C. A., SENEDA, L. M. & BURTON, E. L. 2015. Oral Complications of Cancer Therapy: A Summary Guide for the Clinician. *J Tenn Dent Assoc*, 95, 24–32.
- MOORE, T. B. & SAKAMOTO, K. M. 2005. Topics in pediatric leukemia--hematopoietic stem cell transplantation. *MedGenMed*, 7, 19.
- NAJAF, L., BORGVALL, N., VENNMAN, K. & WALLADBEGI, J. 2023. An extraoral approach to intraoral cooling-a feasibility study in non-cancer patients. *BMC Oral Health*, 23, 1–8.
- NAU, K. C. & LEWIS, W. D. 2008. Multiple myeloma: diagnosis and treatment. *Am Fam Physician*, 78, 853–9.
- PARK, B., YOO, K. H. & KIM, C. 2015. Hematopoietic stem cell expansion and generation: the ways to make a breakthrough. *Blood Res*, 50, 194–203.

-
- PORRATA, L. F. & ADJEI, A. A. 2001. The pharmacologic basis of high dose chemotherapy with haematopoietic stem cell support for solid tumours. *Br J Cancer*, 85, 484–9.
- PORTER, D. L. 2011. Allogeneic immunotherapy to optimize the graft-versus-tumor effect: concepts and controversies. *Hematology Am Soc Hematol Educ Program*, 2011, 292–8.
- PRESTIN, S., ROTHSCILD, S. I., BETZ, C. S. & KRAFT, M. 2012. Measurement of epithelial thickness within the oral cavity using optical coherence tomography. *Head Neck*, 34, 1777–81.
- QIN, R., STEEL, A. & FAZEL, N. 2017. Oral mucosa biology and salivary biomarkers. *Clin Dermatol*, 35, 477–83.
- RADTKE, M. L. & KOLESAR, J. M. 2005. Palifermin (Kepivance) for the treatment of oral mucositis in patients with hematologic malignancies requiring hematopoietic stem cell support. *J Oncol Pharm Pract*, 11, 121–5.
- RAYMOND, B. M. & AGYEMAN-YEBOAH, J. 2023. Nurses' knowledge on assessment and management of cancer therapy-associated oral mucositis. *Nurs Open*, 10, 7292–300.
- RILEY, P., GLENNY, A. M., WORTHINGTON, H. V., LITTLEWOOD, A., CLARKSON, J. E. & MCCABE, M. G. 2015. Interventions for preventing oral mucositis in patients with cancer receiving treatment: oral cryotherapy. *Cochrane Database Syst Rev*, 2015, CD011552.
- ROCKE, L. K., LOPRINZI, C. L., LEE, J. K., KUNSELMAN, S. J., IVERSON, R. K., FINCK, G., LIFSEY, D., GLAW, K. C., STEVENS, B. A., HATFIELD, A. K. & ET AL. 1993. A randomized clinical trial of two different durations of oral cryotherapy for prevention of 5-fluorouracil-related stomatitis. *Cancer*, 72, 2234–8.
- RODRIGUEZ, A. L., TARIMAN, J. D., ENECIO, T. & ESTRELLA, S. M. 2007. The role of high-dose chemotherapy supported by hematopoietic stem cell transplantation in patients with multiple myeloma: implications for nursing. *Clin J Oncol Nurs*, 11, 579–89.
- SHEWACH, D. S. & KUCHTA, R. D. 2009. Introduction to cancer chemotherapeutics. *Chem Rev*, 109, 2859–61.
-

- SHLOMCHIK, W. D. 2007. Graft-versus-host disease. *Nat Rev Immunol*, 7, 340–52.
- SINGH, A. K. & MCGUIRK, J. P. 2016. Allogeneic Stem Cell Transplantation: A Historical and Scientific Overview. *Cancer Res*, 76, 6445–51.
- SONIS, S. T. 2009. Mucositis: The impact, biology and therapeutic opportunities of oral mucositis. *Oral Oncol*, 45, 1015–20.
- SONIS, S. T., EILERS, J. P., EPSTEIN, J. B., LEVEQUE, F. G., LIGGETT, W. H., JR., MULAGHA, M. T., PETERSON, D. E., ROSE, A. H., SCHUBERT, M. M., SPIJKERVET, F. K. & WITTES, J. P. 1999. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. *Cancer*, 85, 2103–13.
- VERA-LLONCH, M., OSTER, G., FORD, C. M., LU, J. & SONIS, S. 2007. Oral mucositis and outcomes of autologous hematopoietic stem-cell transplantation following high-dose melphalan conditioning for multiple myeloma. *J Support Oncol*, 5, 231–5.
- WALLADBEGI, J., DANKIS, M., AYDOGDU, O., JONTELL, M. & WINDER, M. 2023. Moderate temperature reduction is sufficient for prevention of 5-fluorouracil-induced oral mucositis: an experimental in vivo study in rats. *Cancer Chemother Pharmacol*, 91, 67–75.
- WALLADBEGI, J., RABER-DURLACHER, J. E., JONTELL, M. & MILSTEIN, D. M. J. 2023. Hemodynamics of the oral mucosa during cooling: A crossover clinical trial. *Heliyon*, 9, e19958.
- WALLADBEGI, J., GELLERSTEDT, M., SVANBERG, A. & JONTELL, M. 2017. Innovative intraoral cooling device better tolerated and equally effective as ice cooling. *Cancer Chemother Pharmacol*, 80, 965–72.
- WHO. 2020. *Cancer* [Online]. World Health organization <http://www.who.int/news-room/fact-sheets/detail/cancer> [Accessed: 6 November 2025].

APPENDIX

The author **Ibrahim A.** published earlier work under the name **Mahdi A.** Publications listed under **Ibrahim A.** and **Mahdi A.** refer to the same person.

- I. Walladbegi J., Henriksson R., Tavelin B., Svanberg A., Larfors G., Jadersten M., Schjesvold F., **Mahdi A.**, Garmin Legert K., Peterson E. D., Jontell M. Efficacy of a novel device for cryoprevention of oral mucositis: a randomized, blinded, multicenter, parallel group, phase 3 trial. *Bone Marrow Transplantation* 2022;57:191–7.
- II. **Mahdi A.**, Stubner J., Bergling M., Jontell J., Walladbegi J. Can cryoprevention of oral mucositis be obtained at a higher temperature? *Clinical Oral Investigations* 2021;25:4519–26.
- III. **Ibrahim A.**, Camci E., Khairallah L., Jontell M., Walladbegi J. Cryopreventive temperatures prior to chemotherapy. *Medical Oncology* 2023;40:1–7.
- IV. **Ibrahim A.**, Mahmoud D., Mavandadipur H., Walladbegi J. Interrater Reliability in the Assessment of Oral Mucositis among Patients Receiving High-Dose Chemotherapy: A Multicenter Comparison between Specialized Dentists and Registered Nurses. *BMC Cancer* 2025;25:1874–7.