Master thesis: Chronic Oral Graft-versus-Host Disease

Clinician- and patient-rated outcomes and their impact on Quality of Life

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Abstract

Introduction

Chronic Graft-versus-Host disease (cGvHD) is a complication of allogeneic hematopoietic stem cell transplantation (HSCT), which diminishes patients' quality of life (QoL). The oral cavity is often affected, causing mucosal changes (erythema, pseudomembranous ulcerations, lichenoid and hyperkeratotic changes), oral dryness, and sclerosis. Previous studies discussed the signs and symptoms and pathophysiology of oral cGvHD and its management. However, the association between objective and subjective oral cGvHD assessment tools and the influence of oral cGvHD on patients' QoL has hardly been studied.

Aims

To study any associations between objective and subjective oral cGvHD assessments and to study the influence of oral cGvHD on patients' QoL.

Methods

Patients with oral cGvHD referred to the Department of Oral and Maxillofacial Surgery, Academic Medical Center Amsterdam (AMC), between September 2015 and June 2016 were included. Patients filled out questionnaires on oral symptoms and QoL. Mucosal changes were scored, salivary flow rates (stimulated and unstimulated) and mouth opening were measured.

Results

In total 16 patients were included. A strong correlation was found between objective and subjective oral dryness ($r = -0.92$, $p<0.01$). However, objective and subjective assessments of oral mucosal cGvHD did not correlate. A significant correlation was found between QoL ratings and experiencing pain and discomfort in the oral cavity and having trouble eating ($r = -0.599$ $p = 0.014$ and $r = -0.614$ $p = 0.011$ respectively). No significant correlation was found between oral dryness, mucosal changes, and sclerosis associated with oral cGvHD.

Conclusion

We found that objective and subjective oral dryness assessments were strongly associated. In contrast, objective and subjective assessments of mucosal oral cGvHD did not correlate, underlining the importance of including patient-reported outcomes. No associations could be identified between oral dryness, mucosal cGvHD and sclerosis, suggesting that these features of oral cGvHD may occur in isolation. Having trouble eating and experiencing oral pain and discomfort were associated with diminished QoL. Despite of the small sample size and the need for larger prospective studies, our results have implications for identifying oral cGvHD manifestations and its management.

Content

1. Introduction

Chronic Graft versus Host disease (cGvHD) is a significant complication of allogeneic hematopoietic stem cell transplantation (HSCT) with high morbidity among patients and thus potentially significantly affecting their quality of life (QoL) [28]. Many organs can be involved in this disease including the mouth. In 48%-72% of allogeneic HSCT recipients suffering from cGvHD, the oral cavity is affected[29]. When manifesting in the mouth it is referred to as oral cGvHD. The mouth may be the only site of involvement and the oral cavity can be the site of persistent activity after resolution of cGvHD affecting other sites. Oral mucosal changes like erythema and ulcerations may be associated with pain and discomfort. Oral intake is often reduced because of pain or sensitivity associated with these mucosal changes and because of alterations in taste[3]. However, Fall-Dickson et al (2010) found no association between health related quality of life (HRQL) and oral mucosal cGvHD severity[12]. Not only the oral mucosa but also the major and minor salivary glands can be affected by cGvHD[25]. Salivary gland involvement leads to destruction of secretory acini and ducts, resulting in oral dryness that may be bothersome for patients and significantly increases the risk of developing dental caries. Previously, an association was found between poorer Health-Related QoL (HRQoL) and oral dryness[12]. However, our present understanding of how clinician-rated and patient-reported signs and symptoms of oral cGVHD relate to each other and their impact on patient's QoL is still very limited.
The aim of the study presented in this thesis is to examine the level of association between objective and subjective assessments of oral cGvHD, to assess whether different manifestations of cGvHD are related, and to assess whether oral cGvHD symptoms affect patient's perceived oral health and their global QoL.

1.1 Hematopoietic stem cell transplantation

Hematologic malignancies, selected solid tumors, autoimmune diseases and bone marrow failures may be treated with HSCT. Hematopoietic stem cells, extracted from bone marrow and peripheral blood, are the precursors of blood cells. Blood cells play an important role in hemostasis and wound healing (platelets), immunological responses (white blood cells) and oxygen transport (red blood cells)[2].
Stem cells used in HSCT can be of autologous origin (isolated from the patient) or allogeneic (from a related or an unrelated donor). Whereas in the past most hematopoietic stem cells were isolated from bone marrow, more recently these cells are mostly harvested from peripheral blood. In some cases, stem cells are derived from umbilical cord blood. In 2014 over 40,000 HSCTs were performed in Europe; of these 57% were autologous, and 43% were allogeneic HSCTs[33]. The number of transplants increases every year. In 5 years the total number of transplants in Europe increased with 22%; especially due to an increase of the number of

allogeneic transplants. It is to be expected that the number of transplants will continue to rise since HSCT has become a treatment option for an increasing number of diseases and patients. This is largely by the virtue of the development of less toxic preparative regimens making HSCT available to older patients and those having a frail condition[35 36].
Whether autologous or allogeneic stem cells are used depends on the underlying disease for which the patient is treated and the availability of a suitable donor.

1.1.1 Autologous HSCT

Autologous HSCT is the treatment of choice in multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's disease, some autoimmune disorders and amyloidosis[5]. In autologous HSCT recipients, the disease is primarily treated with intensive chemotherapy and/or total body irradiation (TBI). These treatment modalities cause severe and irreversible damage to the bone marrow, thereby eradicating hematopoietic stem cells (myeloablation). Therefore the patient's own stem cells (harvested prior to treatment) are re-administered after chemotherapy and/or TBI to achieve hematologic recovery. In autologous HSCT, GvHD will not occur since the administered stem cells are stem cells derived from the patient itself, and thus no immunological reaction will be mounted [5].

1.1.2 Allogeneic HSCT

Allogeneic HSCT is often the treatment of choice in acute and chronic leukemia, a number of lymphomas and selected types of severe anemia. Prior to transplantation, patients are treated with high dose chemotherapy with or without TBI, in order to eradicate any residual tumor cells (which may be still present after previous chemotherapy), and to obtain immune suppression to prevent rejection from the graft by the host and thereby making engraftment possible. This treatment however, causes major complications and the risk of these complications increases with age. That is why less toxic 'Reduced Intensity Stem cell Transplantation' (RIST), or non-myeloablative (NMA) conditioning protocols have been developed that largely depend on immunological effects to treat the malignancy. These less toxic forms of HSCTs became the treatment of choice in patients above 40 years of age and those with comorbidities. In RIST/NMA HSCT, preparative chemotherapy with or without low dose TBI is administered, causing less severe acute complications[5]. After this conditioning regimen, allogeneic stem cells are administered to the patient and engraftment is awaited[5]. Ideally, the patient's bone marrow will be completely replaced by donor cells to optimally benefit from Graft versus Leukemia/Tumor effect. This is an advantageous effect of allogeneic HSCT, in which the malignant cells of the recipient are attacked by grafted cells derived from the donor[21 38]. A related adverse effect is GvHD. In GvHD, graft-derived cells (especially cytotoxic T-lymphocytes) attack healthy tissues and organs of the host (patient), in the same way they raise an immune response against malignant cells[21]. This of course is an unwanted complication of the

treatment, which can severely impair patients' health. All types of allogeneic HSCT can initiate GvHD. Donor cells derived from peripheral blood, however, provoke GvHD more often and more severely than stem cells harvested from bone marrow[6]. This makes treatment of GvHD even more difficult and prolongs treatment time[5].

1.2 Graft versus host disease

GvHD can be acute or chronic. When defining GvHD signs and symptoms as acute or chronic, chronological, clinical and pathologic features are taken into account. However, when only focusing on time of onset (previous way of classification), the line between acute and chronic GvHD seems to be arbitrary and not practical[38]. The acute form of GvHD (aGvHD) usually sets on between stem cell infusion (day 0 of HSCT) and day 100 post-HSCT[46]. GvHD is diagnosed based on the patient's medical history, the clinical features and when deemed necessary a tissue biopsy. In acute GvHD most often the skin, liver, mouth and gastrointestinal tract are involved. Patients suffer from impaired liver function that causes jaundice (icterus), irritated erythematous skin (maculopapular rash), nausea and diarrhea[31]. Schubert & Correa (2008) reported that 35-60% of aGvHD patients have lichenoid and/or ulcerative oral manifestations[38]. Chronic GvHD most often manifests in the mouth and gastrointestinal tract, liver, skin, lungs, eyes and genital mucosa[30 38]. It may cause a variety of signs and symptoms including dry and irritated skin, ocular dryness (xerophtalmia), oral dryness (hyposalivation/xerostomia), genital mucosal ulceration and dryness, immunosuppression, malabsorption in the intestines, decreased pulmonary function, and sclerosis[3 7 25].

To treat these manifestations patients receive a wide range of medications. Systemic corticosteroids and cyclosporines are administered to suppress the immune system and may be continued for years. Cyclosporine suppresses cGvHD by restraining the proliferation of T cells. Prolonged systemic and/or topical corticosteroid use as well as immunosuppression caused by GvHD itself, makes the patient more susceptible to potentially life-threatening (opportunistic) infections like candidiasis, reactivation of herpes simplex viruses and bacterial infections[43]. Therefore, prophylactic use of antifungals and systemic antiviral medications is indicated. Prolonged systemic use of corticosteroids may impair bone remodeling and osteoporosis may occur[5]. In addition, wound healing may be prolonged and patients may develop a Cushingoid appearance (moon face).

1.2.1 Risk factors for developing cGvHD

Myeloablative conditioning regimens increase the risk of developing GvHD, since these regimens increase donor T cell activation. Particularly, mucosal damage (mucositis) is thought to be associated with increased GvHD risk[13]. NMA and RIST regimens, on the other hand, may decrease GvHD risk[38].

Besides the conditioning regimen prior to HSCT, multiple patient (host) and donor characteristics increase the probability of developing cGvHD. It is essential to achieve a high

degree of immunological similarity between the donor and the host. In order to do so, host and donor are matched, mainly by HLA-matching; the major compatibility complex present on all cells except red blood cells[5]. Even though host and donor are 'HLA matched', other factors including minor HLA-antigens can still induce GvHD[20]. As mentioned earlier, stem cells extracted from peripheral blood carry a greater risk of developing GvHD than cells extracted from the donor's bone marrow, probably because grafts harvested from peripheral blood contain more T cells[5]. Older age of the host and/or the donor also increases the risk. HSCT with stem cells from a matched unrelated donor (MUD) has a greater risk of inducing GvHD than when using stem cells from a matched related donor[38], like a sibling[17]. Grafts obtained from a female donor to a male host induce GvHD more frequently as well[36 38]. Literature suggests that previously endured aGvHD is associated with a significantly greater risk of cGvHD development[23]. However, cGvHD can also develop *de novo,* i.e. without a previous acute phase[34].

1.3 Oral Graft versus Host Disease

1.3.1 Acute Oral Graft versus Host Disease

Preparative regimen-induced damage to oral tissues causes an invasion of inflammatory cells. This activates and induces expansion of donor T-cells, exacerbating tissue damage by the production of inflammatory cytokines (cytokine storm), setting the stage for alloreactive reactions against host cells and tissues[21]. Oral aGvHD is characterized by non-specific mucosal redness and ulceration. It can be difficult to distinguish between oral aGvHD and other causes of mucosal pathologies, like oral mucositis (OM) and infections (for example, with herpes simplex viruses and *Candida albicans*)[45]. Oral manifestations of OM usually improve evidently or disappear at the time of bone marrow engraftment after three to four weeks post-HSCT. When neither infection nor OM seem to be the cause, it is likely that acute oral GvHD causes the oral signs and symptoms. To verify the diagnosis performing a tissue biopsy is an option.

1.3.2 Chronic oral Graft versus Host Disease

The pathogenesis of cGVHD is not yet fully unraveled. In brief, activated donor T-cells cause tissue damage. This activates B-cells and stimulates the production of auto antibodies. In the oral cavity cGvHD may express itself in three ways: mucosal changes, salivary gland GvHD, and sclerosis. Patients do not necessarily suffer from all these manifestations.

Oral cGvHD of the oral mucosa is characterized by erythema, pseudomembranous ulcerations, and lichenoid and hyperkeratotic changes (Figure 1, Figure 2)[24 31 44].

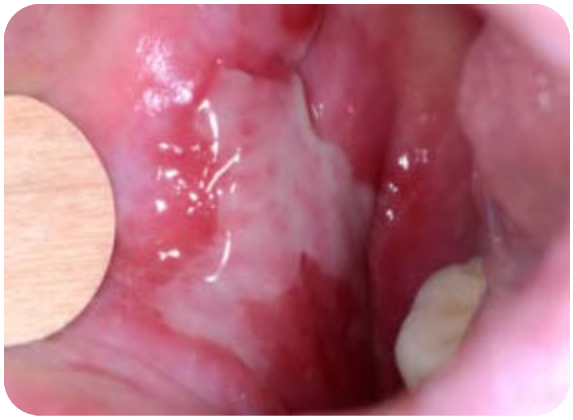

Figure 1.
Erythema and pseudomembranous ulceration on buccal mucosa

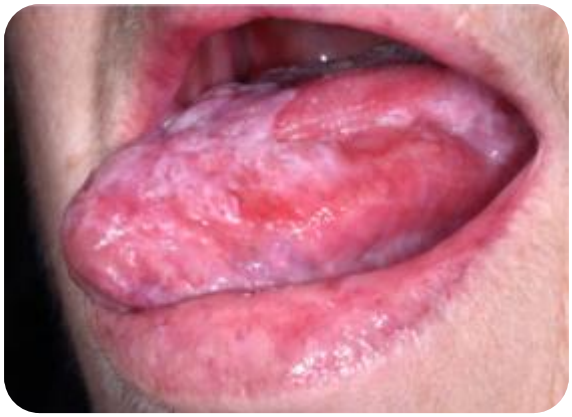

Figure 2.
Hyperkeratotic changes on the tongue

As in Sjögren's syndrome, both salivary glands and lacrimal glands can be involved in cGvHD, which leads to decreased salivary flow, complaints of xerostomia (subjective oral dryness) and xerophtalmia ("sicca syndrome")[25]. Saliva is crucial for a healthy mouth as it balances oral pH, plays a role in the defense against infection, is essential in speech, taste, mastication and swallowing, and helps to protect the teeth against dental decay[32 44]. Decreased salivary flow leads to difficulty speaking, eating and swallowing, forcing patients to change their dietary habits[10 11]. In patients with hyposalivation, dental caries risk increases, particularly in those that also have painful oral mucosa and/or a limited mouth opening (see below), complicating oral hygiene. Moreover, patients are more susceptible to oral mucosal infections, most often with oral Candida spp and herpes simplex viruses[25 32 43]. Prophylactic use of antimycotics and antiviral medications like acyclovir or valacyclovir is therefore indicated[24]. Previous studies have shown a correlation between xerostomia and xerophtalmia in GvHD patients[25]. Diminished salivary function also influences general health. Patients with reduced salivary gland function had significantly lower Body Mass Index values (BMI) than patients with normal salivary flow rates[25].

Furthermore, patients with oral cGvHD are more susceptible to developing squamous cell carcinoma of the oral cavity and lips[43]. Regular oral examination and discouraging smoking and excessive alcohol intake is therefore important. Patients should be routinely evaluated for oral (pre)-malignancies annually. However, when histopathological examination of a lesion shows dysplasia a shorter recall interval is in place[3 9 37].

Sclerosis can affect the skin, muscles and mucosa. Restricted mouth opening can be a sign of scleroderma or mucosal sclerosis [10 11 38]. Sclerosis can also affect the tongue, which makes eating and speech more difficult[10 11]. Intraoral fibrotic bands may be seen, limiting tongue and jaw movement (Figure 3).

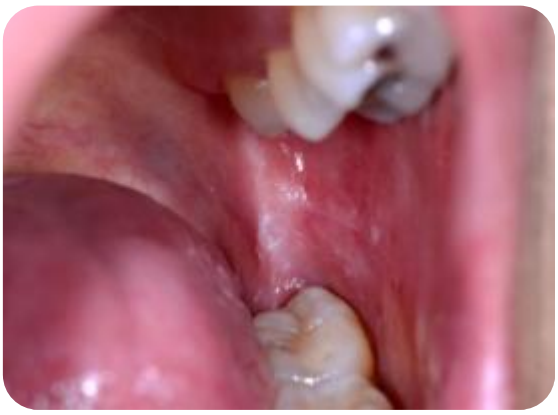

Figure 3.
Fibrotic band

1.3.3 Treatment of oral cGvHD

1.3.3.1 General oral health

Good oral hygiene is crucial, especially in GvHD patients, since oral infection can be a trigger for GvHD and patients are more susceptible to develop dental caries due to diminished salivary output and changes in salivary composition (including decreased levels of immunoglobulins)[9 36 37]. However, oral pain and sensitivity, reduced mouth opening and the general physical condition, like fatigue, can make it very difficult and sometimes even impossible to maintain good oral hygiene[38]. Dental plaque and infections, particularly gingivitis and periodontitis may worsen GvHD by triggering an immunological response. Dental care professionals can play a very important role in the management of oral cGvHD and maintaining oral health as much as possible in these patients. It is therefore necessary to inform dental care professionals about this condition and what they can do to improve these patients' oral health, and with doing so their general wellbeing. Patients with limited salivary flow rates, insufficient oral hygiene, or periodontal diseases should visit the dentist more regularly for a dental check-up including professional cleaning, and management of periodontal diseases. Fluoride applications may be indicated since they are more likely to develop dental caries[24 37].

1.3.3.2 Oral mucosa

Topical corticosteroid gels or solutions like dexamethasone or clobetasol mouth rinses are

prescribed to treat oral mucosal cGvHD[26 44]. Also topical budesonide may have a beneficial effect in the treatment of oral lesions. Topical corticosteroid use causes atrophy and therefore topical tacrolimus (a calcineurin inhibitor) is indicated when the vermillion lips are affected by GvHD. Tacrolimus reduces T-cell activity and cytokine production[26 44].

1.3.3.3 Salivary glands

Since cGvHD can also affect the salivary glands, causing hyposalivation, it is desirable to increase the salivary output. However, increasing salivary production by stimulating salivary glands is not possible if a substantial part of salivary gland tissue is destructed. When there still is (limited) salivary function sugar free gum or candies can increase the salivary flow. Increasing the secretion with stimulating agents like cholinergic agents (pilocarpine or cevimeline) has proven to be efficient in relieving the symptoms[14 45]. Pilocarpine and cevimeline (not available in the Netherlands), however also increase gastric fluid secretion, sweating, and induce sedation. Studies focusing on cevimeline have shown that it can cause severe nausea consequently leading to withdrawal from therapy[14]. In patients with Sjögren's Syndrome, pilocarpine increases the production of saliva and decreases the dry eyes and dry mouth complaints[45]. Cevimeline has also shown to increase the salivary and lacrimal output[34].
Salivary substitutes may relieve oral dryness, however, these products neither contain all the enzymes of natural saliva nor have the same viscosity and taste is not tolerated by all patients[45].
Mucoceles are a manifestation of salivary gland cGvHD. Mucoceles, minor salivary gland blisters filled with mucus, are usually asymptomatic and disappear shortly after eating. However, if mucoceles are not asymptomatic and appear often, topical treatment with steroids is the course of treatment. In exceptional cases, mucoceles need to be surgically removed[41].

1.3.3.4 Photobiomodulation

Local and/or systemic treatment of oral GvHD may not always have the desired effect. Also, immunosuppressive medication increases the risk of opportunistic infections and the development of second primary malignancies. Photobiomodulation (PBM), formerly called low level laser therapy, might be of added value. Previous studies have shown a beneficial effect of PBM on pain relief, inflammation reduction and tissue healing[4 15]. PBM is increasingly used to treat OM in patients treated with chemotherapy and/or radiation therapy involving the head and neck. PBM prevents OM in HSCT recipients[39], and may improve OM symptoms and improve patients' QoL[18 19]. Also, Dabić et al (2016) showed PBM can increase salivary output[8]. In the treatment of oral GvHD, PBM may have a significant potential. Presently, limited literature is available addressing the potential beneficial effect of PBM in these patients. A case series study by Epstein et al (2016), suggested promising first results including significant improvement of oral pain, oral dryness and stiffness following PBM therapy[11].

1.4 Present study

Previous studies into oral cGvHD discussed the signs and symptoms and the pathophysiology of cGvHD, and its management. However, several clinically relevant issues concerning oral cGvHD were not or only partially assessed in these previous studies. Therefore, in the current study we aimed to:

(1) assess the association between objective and subjective symptom measurements;

(2) study whether an association between different manifestations of oral cGvHD (i.e. mucosal, salivary, and sclerotic cGvHD) can be identified;

(3) study the effect of the oral cGvHD symptoms and perceived oral health on global QoL.

2.Materials and Methods

Patients with oral cGVHD complaints attending the AMC- Department of Oral and Maxillofacial Surgery between September 2015 and June 2016 filled in questionnaires regarding oral cGvHD complaints, overall QoL and perceived oral health. Salivary flow rates were determined (unstimulated and stimulated) and interincisal mouth opening was measured to assess signs of sclerosis. Clinically, mucosal changes in the oral cavity were scored.

The Institutional Review Board (METC) of the AMC considered this study as non-invasive and part of patient care and therefore a non-WMO declaration was granted.
All questionnaires and the NIH score forms are attached in the Appendix.

Questionnaires and objective NIH score

Quality of Life

Quality of life was scored using the EORTC QLQ-C30 version 3.0 (European Organization for Research and Treatment of Cancer Quality of life Questionnaire). This questionnaire was developed in 1995 to assess the health related quality of life of cancer patients in 30 items. The questionnaire consists of fifteen subscales; five functioning scales (physical, social, emotional, role and cognitive functioning), a global functioning scale, three symptom scales (fatigue, pain, nausea/vomiting) and six single item scales (appetite loss, shortness of breath, trouble sleeping, diarrhea, obstipation and financial difficulties) (oncoline.nl).

An example item of the EORTC QLQ-C30 of the pain symptom scale is: “Did pain interfere with your daily activities?” An example of the emotional functional scale is: “Did you feel tense?” Questions ‘1’ till ‘28’ are answered with ‘not at all’, ‘a little’, quite a bit’ or ‘very much’, ‘not at all’ is scored as ‘1’, ‘very much’ as ‘4’. A high score indicates severe complaints, a low score little complaints. Questions 29 en 30, forming the subscale ‘global functioning scale’, are scored by the patient on a scale of 1 to 7; score ‘1’ stands for ‘very bad’ and score ‘7’ stands for ‘excellent’. A high score indicates good global functioning; a low score indicates poor global functioning.

Quality of Life related to oral and dental health

The influence of oral and dental problems on QoL was measured using the EORTC QLQ-OH17 and the OHIP-14. The EORTC QLQ-OH17 addresses the influence of oral and dental problems on cancer patients’ QoL in 17 items. The questionnaire was developed and validated by Hjermstad et al [21]. The questionnaire consists of four subscales; pain/discomfort, eating, xerostomia and how patients judge received information prior to treatment about potential oral side effects. An example item of the EORTC QLQ-OH17 of the ‘pain and discomfort’ scale is: “Has your mouth been sensitive to food and drinks?”
Questions are answered with ‘not at all’, ‘a little’, quite a bit’ or ‘very much’; ‘not at all’ is

scored as ‘1’, ‘very much’ as ‘4’. On all subscales a high score indicates severe complaints; a low score indicates little/few complaints.
In 1997 a shorter version of the 49-item OHIP[42] was developed and validated by Slade; the OHIP-14[41]. This 14-item questionnaire contained the dimensions of impact of patients oral health related QoL; pain, psychological discomfort, physical-, social- and psychological disability, functional limitations, handicap and psychological discomfort[37].
An example item of the OHIP-14 questionnaire is: “Have you felt that life in general was less satisfying because of problems with your teeth, mouth or dentures?” Questions are answered with ‘never’, ‘rarely’, ‘occasionally’, ‘rather often’ or ‘very often’; ‘never’ is scored as ‘0’, ‘very often’ as ‘4’. The OHIP-14 is scored as the sum of all items; meaning the score range is 0-56; a higher score indicates more severe complaints.

Chronic oral GvHD

Oral cGVHD was scored according to the objective NIH (National Institutes of Health) score. This score assesses oral mucosal changes and the extent and severity of those changes, scored by the practitioner during a clinical exam[37]. The score range is 0-15; a score of ‘0’ indicates no objective mucosal symptoms, whereas a score of ‘15’ indicates severe oral mucosal symptoms[38].
Patient-reported oral cGvHD was assessed according to the subjective NIH Chronic GVHD Activity Assessment Score. Patient-reported oral dryness, oral pain and oral sensitivity (i.e. during function) during the last week (at the time of filling in the questionnaires) was scored on a 0-10 Likert scale; ‘0’ indicates no dryness/oral pain/oral sensitivity, ’10’ indicates the worst imaginable dryness/oral pain/oral sensitivity[43].

Salivary flow measurements

1) 1) Unstimulated salivary flow was measured for 5 minutes. Patients were asked to swallow and thereafter spit every 30 seconds all the accumulated saliva into a cup. The cups where weighed before and after collecting the saliva. The weight of the cup containing the saliva minus the weight of the cup before collecting the saliva is the weight of the collected saliva. The flow rate per minute was calculated by dividing the weight of the saliva by 5. The salivary flow rate is expressed in ml/min.
2) Stimulated salivary flow was also measured for 5 minutes by chewing on paraffin gum. The stimulated salivary flow was measured the same way as the unstimulated saliva and is also expressed in ml/min. Table 1 displays the interpretation of salivary flow rates measured (unstimulated and stimulated).

Salivary type	Value (ml/min)	Interpretation
Unstimulated whole saliva	>0.5	Hypersalivation
	0.2-0.5	Normal
	0.1-0.2	Low Margin
	<0.1	Hyposalivation
Chewing stimulated whole saliva	>2.0	Hypersalivation
	0.7-2.0	Normal
	0.5-0.7	Low Margin
	<0.5	Hyposalivation

Table 1. Interpretation of salivary flow rates (stimulated and unstimulated)
Source: van Nieuw Amerongen (2004)[32]

Maximal mouth opening

To assess sclerosis of the oral cavity the maximal mouth opening is determined by measuring the interincisal distance. A distance of 40mm is considered a 'normal' mouth opening, <40mm 'below average', and >40mm 'above average'[8].

Statistical analysis

Data analysis was performed using IBM SPSS 20.0.

Several associations were calculated using the Spearmans's correlation coefficient:
- the relationship between salivary flow rates and subjective oral dryness
- the relationship between objective and subjective measurements of oral cGvHD
- the relationship between subjective and objective oral dryness, mucosal GvHD, mouth opening, and oral health questionnaires
- the relationship between oral dryness, mucosal GvHD and sclerosis, and the subjectively reported global QoL

The difference in xerostomia between patients with normal and low objective stimulated salivary flow (<0,5 ml/min i.e. hyposalivation, Table 1) was compared using the independent sample Mann-Whitney U test.

A p-value < 0.05 was considered statistically significant.

3.Results

During the period from September 2015 until June 2016, seventeen consecutive oral cGvHD patients referred to our department were asked to participate in this study. All (17) patients gave their consent to participate. One patient (pt ID 10) was excluded from the study as he appeared to be too ill to complete the questionnaires due to severe cGvHD of the gastrointestinal tract, and passed away shortly after.
Of the remaining 16 patients, 10 were male and 6 were female. The mean age was 54.5 years, ranging from 30 to 69 years. Most patients (12) were treated for leukemia (chronic or acute), and the majority of patients (12) were treated with a non-myeloablative conditioning regimen. Table 2 shows an overview of the patient characteristics.

Pt ID	Gender	Age (Yrs)	Date of transplant (Month/year)	HSCT	Conditioning (myeloalative/non-myeloablative)	Previous oral aGvHD	Disease	GvHD elsewhere
1	M	66	10/2007	MRD	Non-Mye, Fludarabine + TBI	Yes	AML	Oropharynx, Eyes, Skin, Lungs, GIT (acute)
2	F	30	2010	MUD	Mye	Yes	ALL	Oropharynx, Eyes, Skin
3	M	57	2011	MRD	Non-Mye	No	MDS	Skin, eyes
4	M	65	01/2012	MRD	Non-Mye, Fludarabine+ TBI	No	AML	Liver, Skin, Joints
5	M	65	02/2014	MUD	Non-Mye, Fludarabine + TBI	Yes	MDS-AML	Skin, Eyes
6	F	68	08/2013	MUD	Non-Mye, Fludarabine + TBI	No	CLL	Oropharynx, Skin, Eyes
7	M	31	10/2014	MUD	Semi –Mye, Fludarabine + cyclophosphamide + TBI	Yes	AML	Oropharynx, Skin, Eyes
8	F	69	02/2015	MRD	Non-Mye, Fludarabine + TBI	Yes	ALL	Skin, Eyes
9	M	54	5/2011	MUD	Non-Mye, TBI	Yes	CLL	Skin, Lungs
11	M	60	4/2015	MUD	Non-Mye, Fludarabine + TBI	Yes	AML	Oropharynx, Skin, Liver
12	F	38	7/2014	MRD	Non-Mye, Fludarabine + TBI	No	ALL	Oropharyn, Skin, GIT
13	F	55	08/2013	MRD	Non-Mye, Fludarabine + TBI	No	NHL	Skin
14	M	56	07/2015	MUD	Fludarabine + TBI	Yes	NHL	GIT
15	M	57	10/1991	MRD	Mye	Yes	AML	Skin,Liver, GIT
16	F	43	2005	MUD	Mye,Cyclophosphamide + TBI	No	CML	Skin, eyes
17	M	58	02/2013	MRD	Non-Mye, Fludarabine + TBI	Yes	FL	Lung, GIT

Table 2 Patient characteristics.
Abbreviations: aGVHD: acute Graft versus Host disease, ALL: acute lymphatic leukemia, AML: acute myeloid leukemia, CLL: chronic lymphatic leukemia, CML: chronic myeloid leukemia, F: female, FL: follicular lymphoma, GIT: gastro intestinal tract, HSCT: hematopoietic stem cell transplantation, MDS: myelodysplastic syndrome, M: male, Mye: myeloablative, MRD: matched related donor, NHL: non Hodgkin lymphoma, TBI: total body irradiation, UK: Unknown.

3.1 The level of agreement between objective and subjective oral cGvHD assessments

3.1.1 Dry mouth

A significant correlation was found between the score on the OH17 'xerostomia' subscale and oral dryness (Table 3). We also found a significant negative correlation between the subjective assessments and the objective salivary flow measurements, both stimulated and unstimulated (Table 3). This means a higher salivary flow rate (stimulated and unstimulated) is associated with lower scores on the oral dryness scale and the OH17 'xerostomia' subscale. For stimulated salivary flow this association was evidently stronger than for unstimulated salivary flow (Table 3).

OH17	0.82**	-0.64**	-0.84**
	Oral Dryness	-0.69**	-0.92**
		US	0.81**
			SS

Table 3.
Correlations between objective (stimulated and unstimulated salivary flow) and subjective oral dryness assessments (OH17 'xerostomia' subscale and oral dryness scores).
** $p < 0.01$

Abbreviations:
SS: stimulated saliva
US: unstimulated saliva

To further assess the association between objective stimulated salivary flow and subjective measurements, we classified the patients into two groups: stimulated salivary output below 0.5 ml/min (hyposalivation threshold) and salivary output equal or above 0.5 ml/min, respectively (Table 1). A Mann-Whitney U-test showed that OH17 'xerostomia' scores were significantly higher in the low saliva group (Mean = 61.11, SD = 25.09, N= 6) than in the high saliva group (Mean = 16.67, SD = 19.92, N= 8), $p = 0.005$, which indicated that patients with low stimulated salivary flow experienced more xerostomia complaints. Moreover, patients in the low saliva group scored higher on the oral dryness scale (Mean = 7.67, SD = 2.56, N= 6) and thus experienced more oral dryness compared to the patients in the high saliva group, (Mean = 1.63, SD = 2.56, N= 8), $p = 0.003$.
The distribution of the scores of the OH17 'xerostomia' subscale and the oral dryness scale in both groups are shown in a waterfall plot in Figure 4.
Both stimulated and unstimulated salivary flows were evidently associated with subjective oral dryness assessments. Stimulated salivary flow however, showed the strongest association.

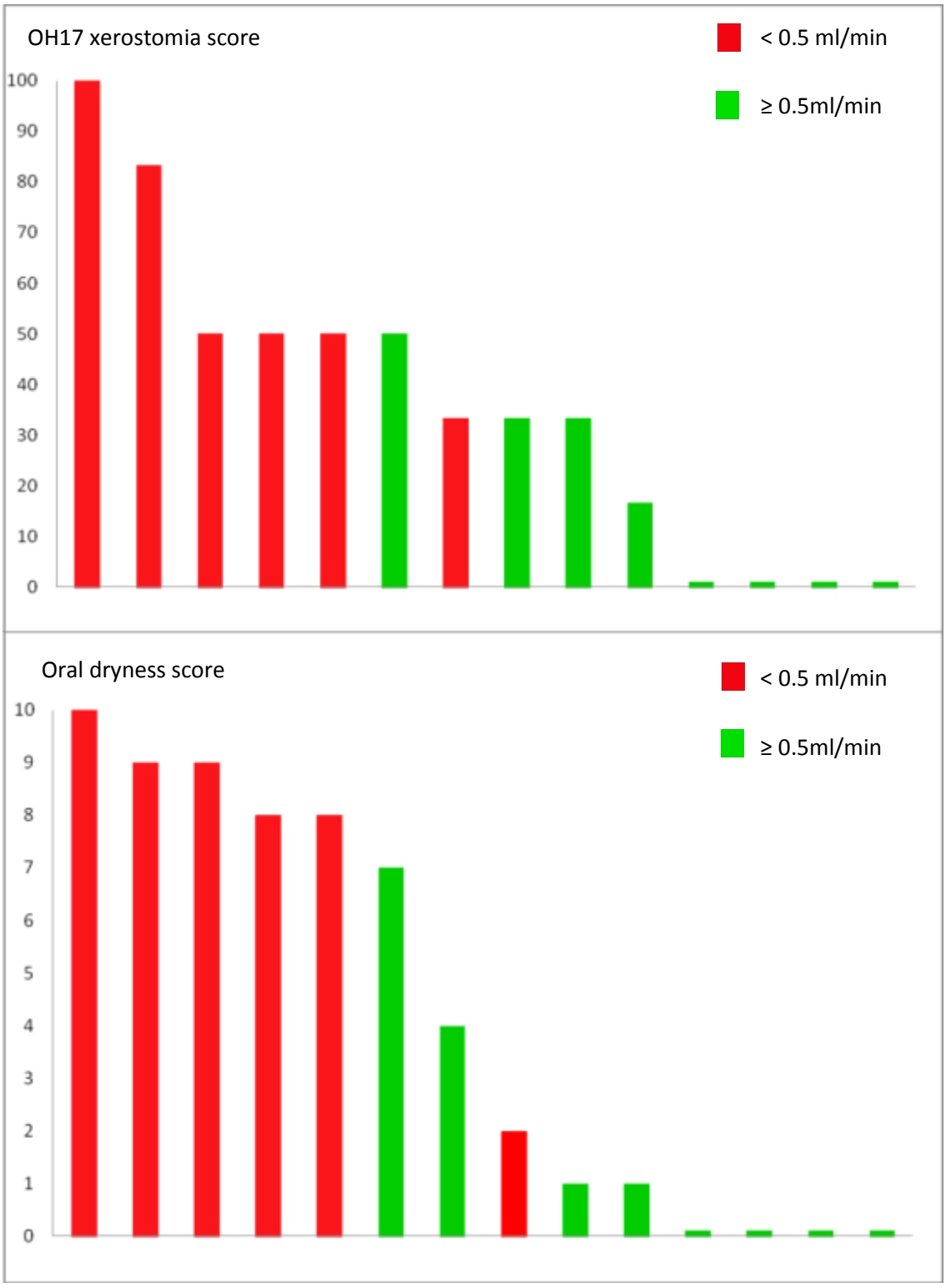

Figure 4

Y-axis: scores on OH-17 'xerostomia subscale respectively oral dryness score. X-axis: Patients ranked from high scores to low scores. Group 1 (SS < 0.5ml/min, i.e. hyposalivation) is colored red, group 2 (SS ≥ 0.5ml/min) is colored green. High scores are significantly more frequent in the hypo salivation group (red) than in the non-hypo salivation group (green).

3.1.2 Mucosal changes

For analyzing the association between objectively scored oral cGvHD and multiple subjective measurements of oral discomfort (other than oral dryness) we calculated Spearman's correlations between the NIH score (objective), the OHIP-14 , EORTC QLQ-OH17 'eating' and 'pain and discomfort' subscale, oral pain and oral sensitivity scale (subjective). The results are shown in Table 4.

NIH	0.432†	-0.060	0.137	0.273	0.077
	oral sensitivity	0.482†	0.481†	0.541*	0.562*
		Oral pain	0.330	0.414	0.468†
			OH17 PD	0.354	0.562*
				OH17 EA	0.715**
					OHIP- 14

Table 4. Correlations between NIH GvHD score and assessments of oral pain and discomfort (oral sensitivity, oral pain, OH17 'pain and discomfort' subscale, OH17 'eating' subscale and OHIP-14 scores)
Spearman correlation coefficients were shown.
Notes:
† 0.05> P <0.1
* P <0.05
** P < 0.01

As shown in table 4, a significant correlation was found between the oral sensitivity score and the 'eating' subscale of the OH17 (r = 0.541 p = 0.030) and the OHIP-14 score (r = 0.562 p = 0.023). This means that patients' oral sensitivity scores are moderately associated with having trouble eating and oral and dental health. Patients that report more oral sensitivity are likely to have more trouble eating and to judge their oral health as worse. Moreover, for oral sensitivity a trend towards statistical significance was observed with the OH17 'pain and discomfort' subscale (p= 0.059).
Except for a trend towards a statistically significant correlation between the objectively scored cGvHD and the oral sensitivity score we did not find any association between the objectively scored cGvHD and subjective assessments. It seems like the degree of visible mucosal changes and the degree of discomfort a patient experiences are not associated.

3.2 Association between oral cGvHD manifestations

3.2.1 Mucosal changes and oral dryness

We hypothesized that mucosal changes might occur simultaneously with reduced salivary flow. Objectively scored mucosal cGvHD was significantly correlated with salivary flow; r = 0.626 p =

0.017 for stimulated salivary flow, and r = 0.499 p = 0.049 for unstimulated salivary flow. Patients with more severe objective mucosal cGvHD had a higher salivary flow rate.
We found no association between subjective parameters of oral dryness and oral mucosal pain and discomfort.

3.2.2 Mouth opening, mucosal oral cGvHD, and oral dryness
For mouth opening and mucosal changes no association was seen. Also, for mouth opening and subjective oral dryness assessments (oral dryness score and OH17 'xerostomia' subscale) no significance correlation was found (r = -0.553, p = 0.062 and r = -0.51, p = 0.09 respectively). It appears that sclerosis as a symptom of oral cGvHD is not connected to other oral symptoms.

3.3 The influence of cGvHD symptoms and perceived oral health on the global QoL

We did find a significant association between oral sensitivity and OHIP-14 scores and OH17 'eating' subscale; r = 0.562 p = 0.023 and r = 0.541 p = 0.030 respectively. The OHIP-14 and OH17 'eating' scale were strongly associated (r = 0.715 p = 0.02), just as the OHIP-14 and the 'pain and discomfort' scale were significantly associated (r = 0.562 p = 0.024). No association was found between oral dryness (objective and subjective) and OHIP-14 scores and OH17 scores, except for the 'xerostomia' subcale (described in 3.1.1). Also, for mouth opening and OHIP-14 scores and OH17 scores no association was found.
The OH17 subscales 'pain and discomfort' and 'eating' were significant negatively associated with global QoL; r = -0.599 p = 0.014 and r = -0.614 p = 0.011 respectively. This means a higher score on the OH17 subscales (indicating more pain and discomfort and more trouble eating) was associated with a lower global QoL rating. However, for the symptom assessments (oral dryness, oral sensitivity and oral pain) and salivary output, no association was found. For global QoL we found an evident association with the functioning subscales.

4. Discussion

The main goals of this study were to characterize the association between objective and subjective oral cGvHD assessments, to assess whether different manifestations of cGvHD are related, and to assess whether oral cGvHD symptoms affect oral health perceived by patients and their global QoL.

The most important finding of our study was that objective assessment of cGvHD of the oral mucosa was not related to subjective oral GvHD assessments. This indicates that oral GvHD can be more extensive than can be observed directly. We noticed that what we observed in the oral cavity and what the patient reported did not always agree and could even be contrary. In some cases, large lesions may cause little discomfort while, on the other hand, small blisters may cause severe complaints of pain and diminish eating. Although assessing objective diagnostic clinical signs of cGvHD (i.e. lichenoid oral mucosal changes) is an important tool to guide physicians to the diagnosis of cGvHD[27] and is also useful to objectify progression of disease and effects of treatment, our results strongly suggest that both objective and subjective features should be taken into account for the management of oral cGvHD. This is particularly important because current management options are merely palliative and aimed to alleviate patient's symptoms.

We observed a strong association between objective and subjective oral dryness. Asking patients to judge their salivary flow seemed to be a reliable tool to assess oral dryness in the cohort we studied. This however, is not in accordance with previous studies, reporting that objective measurements do not necessarily correlate with oral dryness perceived by patients[16] [21]. This may be explained by technical aspects of taking salivary tests, adaption by patients to having less saliva or qualitative changes of the salivary composition[44].

Stimulated salivary flow showed the strongest association with subjective oral dryness assessments. It might be that the feeling of a dry mouth is best reflected by the stimulated salivary flow since patients notice oral dryness and salivary changes mostly during function, for example since salivary flow is stimulated during eating or speaking. It might therefore be that determining the stimulated salivary flow is of greater diagnostic value than the unstimulated salivary flow. The added value of the objective salivary flow measurements in clinical care is the possibility of repeating the measurements at a later time to compare these new values with previously determined salivary flow rates in order to monitor the progression of diminished salivary output or objectifying the effect of treatment. Since subjective and objective assessments of oral dryness correlated well, assessment of subjective oral dryness (through questionnaires or a 10 point Likert scale) might be a reasonable alternative to objective salivary

flow test in case GvHD patients are unable to perform a salivary flow test because of painful lesions or incapability of chewing paraffin gum due to soreness.

For oral pain and oral sensitivity to foods and drinks, we did not find an association. This is in accordance with other reports[44]. Patients may report no pain in rest, but may experience intensive pain upon function (e.g., speaking, eating, drinking, oral hygiene measures etc). It should be noted, that oral mucosal sensitivity is common in patients with oral cGvHD, and not limited to patients with oral ulceration[40].

We found no association between subjective mucosal cGvHD and oral dryness (objective and subjective). This is in accordance with the results reported by Fall-Dickson et al (2010)[12]. For the objective mucosal changes score however, we identified a significant positive correlation with salivary flow; i.e. lower salivary flow rates were correlated with lower cGvHD scores. Based on findings from Imanguli et al (2010) who reported no correlation between mucosal cGvHD and salivary involvement[25], we anticipated finding no correlation or a negative correlation as saliva may protect against mucosal lesions. It is possible, that the time passed since HSCT has an effect, since oral GvHD may affect the mucosa first and destruction of secretory salivary gland cells, severely enough to substantially affect salivary output, takes time. Patients will then score high on the NIH score and high-average on the salivary flow rate test. It is also possible that as the salivary glands are attacked and their function degrades, the mucosal lesions heal and mucosal changes reduce. Patients will then have lower scores on the NIH GvHD rating and salivary flow rates will decrease.
It is thus imperative to assess oral dryness in all oral cGvHD patients, including patients with limited symptoms of oral mucosal cGvHD. Ideally both objective and subjective dryness are recorded. Otherwise hyposalivation can be unnoticed by the dental care professional and proper preventative oral care will not be provided, like fluoride application and more frequent dental checkups. In addition, symptoms may not be left unpalliated. However, as noted above, if it is not possible to conduct a salivary flow rate test, our results indicated a merit of evaluating patient-reported oral dryness.

It has been noted by Treister et al (2012) that mouth opening may also be reduced when extensive buccal reticular changes associated with mucosal cGvHD are present[44]. However, we did not find decreased maximal mouth opening to be associated with other cGvHD features, including mucosal cGvHD. In our patients, decreased mouth opening was more likely caused by primary sclerotic cutaneous cGvHD or secondary to mucosal scarring. It appeared that sclerosis is a feature of oral cGvHD that is not connected to other oral symptoms, which is in accordance with the findings of Imanguli et al (2010)[25].

We did find a significant association between oral sensitivity and oral HR-QoL (both the OHIP-14 scores and OH17 ‘eating’ subscale). In addition, the OHIP-14 and OH17 ‘eating’ scale were

strongly associated. Similarly, the OHIP-14 score and the OH17 'pain and discomfort' scale were significantly associated. No association was found between oral dryness (objective and subjective), and higher OHIP-14 scores (indicating a poorer oral HR-QoL). In contrast, Imanguli and coworkers reported that salivary gland dysfunction was associated with higher OHIP-14 scores[25].

The OH17 subscales 'pain and discomfort' and 'eating' were significantly negatively associated with global QoL. A higher score on the OH17 subscales for pain and discomfort and having more trouble eating was associated with a lower global QoL rating. For mucosal cGvHD, oral dryness and reduced mouth opening we were not able to identify an association with global QoL. This is in accordance with the results reported by Fall-Dickson et al who found no association between oral mucosal cGvHD and HR-QoL[12]. In contrast, they reported an association between oral dryness and poorer HR-QoL.

In conclusion, in this study involving a small number of patients, objective and subjective mucosal cGvHD assessments were not found to be related, underlining the need for performing both assessments. Furthermore, subjective awareness of oral dryness and objective salivary flow measurements were significantly associated. No associations were found between oral mucosal cGvHD, oral dryness, and sclerosis, indicating that these can be considered as separate manifestations of oral cGvHD. Having trouble eating and experiencing oral pain and discomfort were associated with diminished QoL. Despite the need for larger prospective studies, our results have implications for identifying oral cGvHD manifestations and its management.

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Appendix

Dutch

EORTC QLQ-C30

(Version 3.0)

QLQnr. Patientnr.

Datum: Dag . Maand . Jaar

Wij zijn geïnteresseerd in bepaalde dingen over u en uw gezondheid. Wilt u alle vragen beantwoorden door het vakje aan te kruisen dat het meest op u van toepassing. Er zijn geen "juiste" of "onjuiste" antwoorden. De informatie die u geeft strikt vertrouwelijk worden behandeld.

	Helemaal niet	Een beetje	Nogal	Heel erg
1. Heeft u moeite met het doen van inspannende activiteiten zoals het dragen van een zware boodschappentas of een koffer?	☐	☐	☐	☐
2. Heeft u moeite met het maken van een lange wandeling?	☐	☐	☐	☐
3. Heeft u moeite met het maken van een korte wandeling buitenshuis?	☐	☐	☐	☐
4. Moet u overdag in bed of op een stoel blijven?	☐	☐	☐	☐
5. Heeft u hulp nodig met eten, aankleden, uzelf wassen of naar het toilet gaan?	☐	☐	☐	☐

Gedurende de afgelopen week:	Helemaal niet	Een beetje	Nogal	Heel erg
6. Was u beperkt bij het doen van uw werk of andere dagelijkse bezigheden?	☐	☐	☐	☐
7. Was u beperkt in het uitoefenen van uw hobby's of bij andere bezigheden die u in uw vrije tijd doet?	☐	☐	☐	☐
8. Was u kortademig?	☐	☐	☐	☐
9. Heeft u pijn gehad?	☐	☐	☐	☐
10. Had u behoefte om te rusten?	☐	☐	☐	☐
11. Heeft u moeite met slapen gehad?	☐	☐	☐	☐
12. Heeft u zich slap gevoeld?	☐	☐	☐	☐
13. Heeft u gebrek aan eetlust gehad?	☐	☐	☐	☐
14. Heeft u zich misselijk gevoeld?	☐	☐	☐	☐
15. Heeft u overgegeven?	☐	☐	☐	☐

Wilt u a.u.b. naar de volgende bladzijde gaan

QLQnr. Patientnr.

Gedurende de afgelopen week:

	Helemaal niet	Een beetje	Nogal	Heel erg
16. Had u last van obstipatie? (was u verstopt)?	☐	☐	☐	☐
17. Had u diarree?	☐	☐	☐	☐
18. Was u moe?	☐	☐	☐	☐
19. Heeft pijn u gehinderd in uw dagelijkse bezigheden?	☐	☐	☐	☐
20. Heeft u moeite gehad met het concenteren op dingen, zoals een krant lezen of televisie kijken?	☐	☐	☐	☐
21. Voelde u zich gespannen?	☐	☐	☐	☐
22. Maakte u zich zorgen?	☐	☐	☐	☐
23. Voelde u zich prikkelbaar?	☐	☐	☐	☐
24. Voelde u zich neerslachtig?	☐	☐	☐	☐
25. Heeft u moeite gehad met het herinneren van dingen?	☐	☐	☐	☐
26. Heeft uw lichamelijke toestand of medische behandeling uw familieleven in de weg gestaan?	☐	☐	☐	☐
27. Heeft uw lichamelijke toestand of medische behandeling u belemmerd in uw sociale bezigheden?	☐	☐	☐	☐
28. Heeft uw lichamelijke toestand of medische behandeling financiële moeilijkheden met zich meegebracht?	☐	☐	☐	☐

Wilt u voor de volgende vragen het getal tussen 1 en 7 omcirkelen dat het meest op u van toepassing is.

29. Hoe zou u uw algehele gezondheid gedurende de afgelopen week beoordelen?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Erg slecht Uitstekend

30. Hoe zou u uw algehele "kwaliteit van het leven" gedurende de afgelopen week beoordelen?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Erg slecht Uitstekend

10354

Dutch

EORTC QLQ-OH17

QLQnr. Patientnr.

Datum: Dag . Maand . Jaar

Soms zeggen patiënten dat ze volgende klachten of problemen hebben. Wilt u aangeven in welke mate u deze symptomen of problemen gedurende de afgelopen week heeft ervaren? Wilt u alle vragen beantwoorden door het vakje aan te kruisen dat het meest op u van toepassing.

Gedurende de afgelopen week	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
31. Heeft u pijn aan uw tandvlees gehad?	☐	☐	☐	☐
32. Heeft u problemen met bloedend tandvlees gehad?	☐	☐	☐	☐
33. Heeft u wondjes op uw lippen gehad?	☐	☐	☐	☐
34. Heeft u problemen gehad met uw gebit?	☐	☐	☐	☐
35. Was uw mond gevoelig?	☐	☐	☐	☐
36. Heeft u pijnlijke mondhoeken gehad?	☐	☐	☐	☐
37. Heeft u een droge mond gehad?	☐	☐	☐	☐
38. Was uw speeksel kleverig?	☐	☐	☐	☐
39. Was uw mond gevoelig voor voedsel en drank?	☐	☐	☐	☐
40. Was de smaak van voedsel en drank anders dan u gewend was?	☐	☐	☐	☐
41. Heeft u problemen gehad bij het eten van vast voedsel?	☐	☐	☐	☐
42. Heeft u problemen gehad om van maaltijden te genieten?	☐	☐	☐	☐

Tijdens uw huidige ziekte of behandeling (niet alleen de afgelopen week) :	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
43. Heeft u zich zorgen gemaakt over de gezondheid van uw gebit of mond in de toekomst?	☐	☐	☐	☐
44. Heeft u informatie gekregen over mogelijke problemen aan gebit of mond?	☐	☐	☐	☐
45. Was u tevreden over de hoeveelheid informatie die u kreeg over mogelijke problemen aan gebit of mond?	☐	☐	☐	☐

Gedurende de afgelopen week:	**Ja**	**Nee**
46. Droeg u een kunstgebit?	☐	☐

U hoeft vraag 47 alleen te beantwoorden indien u een kunstgebit draagt:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
47. Heeft u problemen gehad met een slecht passend kunstgebit?	☐	☐	☐	☐

Patiënt-gerapporteerde ernst van chronische GVHD

Graag aangeven hoe erg de onderstaande symptomen aanwezig waren gedurende de laatste **7** dagen.
Alstublieft een getal tussen de 0 (symptoom is niet aanwezig) en de 10 (ergst voorstelbare symptomen) omcirkelen.

1. De DROOGHEID van uw MOND op het ergste moment ?

0 1 2 3 4 5 6 7 8 9 10

niet aanwezig ergst voorstelbaar

Droogheid: gevoel van verminderd bevochtigde mond

2. De PIJN in uw MOND op het ergste moment?

0 1 2 3 4 5 6 7 8 9 10

niet aanwezig ergst voorstelbaar

Pijn: pijn die aanwezig was zonder dat u sprak, iets at, dronk of uw mond spoelde

3. De GEVOELIGHEID van uw MOND op het ergste moment?

0 1 2 3 4 5 6 7 8 9 10

niet aanwezig ergst voorstelbaar

Mondgevoeligheid: irritatie of ongemak door eten of drinken (gekruid, warm, zuur, alcohol ed.) of tandpasta dat u normaal gesproken goed kon verdragen

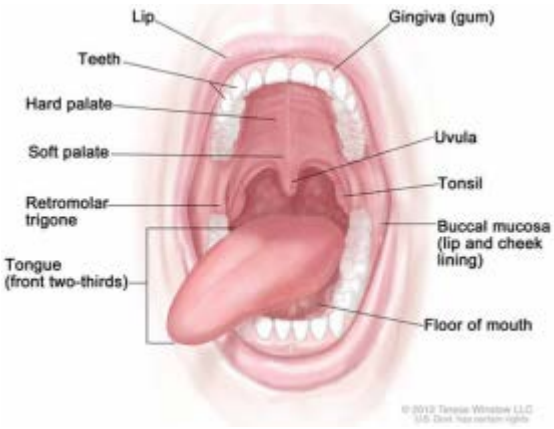
Vragenlijst over tandheelkundige klachten en hun gevolgen (Nederlandse vertaling van de OHIP-14*)

Wilt u bij ieder van de onderstaande klachten en problemen nagaan hoe vaak u er gedurende de afgelopen maand last van heeft gehad, en wilt u dan het antwoord omcirkelen dat het meest van toepassing is.

		nooit	zelden	af en toe	tamelijk vaak	erg vaak
1.	Heeft u moeilijkheden gehad met het uitspreken van bepaalde woorden vanwege problemen met uw gebit, mond of gebitsprothese?	1	2	3	4	5
2.	Heeft u het gevoel gehad dat uw smaakvermogen is afgenomen vanwege problemen met uw gebit, mond of gebitsprothese?	1	2	3	4	5
3.	Heeft u pijn in uw mond gehad?	1	2	3	4	5
4.	Heeft u moeite gehad om bepaald voedsel te eten vanwege problemen met uw gebit, mond of gebitsprothese?	1	2	3	4	5
5.	Heeft u zich onzeker gevoeld vanwege uw gebit, uw mond of gebitsprothese?	1	2	3	4	5
6.	Heeft u zich gespannen gevoeld vanwege problemen met uw gebit, mond of gebitsprothese?	1	2	3	4	5
7.	Is de samenstelling van uw voeding onbevredigend geweest vanwege problemen met uw gebit, mond of gebitsprothese?	1	2	3	4	5
8.	Heeft u maaltijden moeten onderbreken vanwege problemen met uw gebit, mond of gebitsprothese?	1	2	3	4	5
9.	Heeft u moeite gehad om zich te ontspannen vanwege problemen met uw gebit, mond of gebitsprothese?	1	2	3	4	5
10.	Heeft u zich een beetje opgelaten gevoeld vanwege problemen met uw gebit, mond of gebitsprothese?	1	2	3	4	5
11.	Bent u wat prikkelbaar geweest tegen andere mensen vanwege problemen met uw gebit, mond of gebitsprothese?	1	2	3	4	5
12.	Heeft u moeite gehad met het uitvoeren van uw dagelijkse bezigheden vanwege problemen met uw gebit, mond of gebitsprothese	1	2	3	4	5
13.	Heeft u het gevoel gehad dat het leven in het algemeen minder bevredigend was door problemen met uw gebit, mond of gebitsprothese?	1	2	3	4	5
14.	Heeft u totaal niet kunnen functioneren vanwege problemen met uw gebit, mond of gebitsprothese?	1	2	3	4	5

*** vertaling M.J. van der Meulen, F. Lobbezoo**

scorelijst voor chronische GVHD



Mucosale verandering	Geen aanwijzingen voor cGVHD		Mild		Matig		Ernstig	
Roodheid	geen	**0**	Milde of matige roodheid (<25%)	**1**	Matige (≥25%) of ernstige roodheid (<25%)	**2**	Ernstige roodheid (≥25%)	**3**
Lichenoid	geen	**0**	Hyperkeratotische veranderingen (<25%)	**1**	Hyperatotische veranderingen (25%-50%)	**2**	Hyperatotische veranderingen (50%)	**3**
Ulcers	geen	**0**	geen	**0**	Ulcers ≤20% oppervlak	**3**	Ernstige ulceraties (>20%)	**6**
Mucoceles*	geen	**0**	1-5 mucoceles	**1**	6-10 verspreide mucoceles	**2**	Meer dan 10 mucoceles	**3**
			* Mucoceles alleen gescoord voor onder-lip en zachte palatum				**Totale score voor alle mucosale veranderingen**	