Oral Epithelial Dysplasia & Squamous Cell Carcinoma Following Allogeneic Hematopoietic Cell Transplantation

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Abstract

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Oral Medicine

Background: Improved survival after allogeneic hematopoietic stem cell transplantation (alloHCT) is associated with a greater incidence of secondary posttransplant malignancies, including oral squamous cell carcinoma (OSCC).

Aim: Our study aimed to evaluate patient demographics, characteristic features, clinical outcomes, and prevalence of OSCC risk factors in patients diagnosed with OSCC and/or oral epithelial dysplasia (OED) post-alloHCT.

Methods: A retrospective chart review was completed to examine patients treated with allogeneic hematopoietic cell transplantation (alloHCT) at Fred Hutchinson Cancer Research

Center (FHCRC)/Seattle Cancer Care Alliance (SCCA) between 1969 and 2018. Cases of oral squamous cell carcinoma (OSCC) and oral epithelial dysplasia (OED) were identified through the Gateway database. The clinical characteristics were reviewed via chart notes in Optic Web Library and electronic medical records via Epic Hyperspace. Descriptive statistics were used to summarize the general characteristics of the data variables. Overall survival was calculated from the date of diagnosis of OSCC to the date of death. The mortality risk was calculated after adjusting for covariates.

Results: We identified 84 cases of OSCC and 10 cases of OED in 78 subjects treated with alloHCT. The median time from alloHCT to each diagnosis of OSCC/OED was 12.0 years (range 0.8-30.0 years). OSCC lesions were frequently observed on the ventrolateral surface of the tongue (N=23), followed by the buccal mucosa (N=10), the labial mucosa (N=8), and the gingiva (N=7). Same-site lesion recurrence was documented in 25.6% of cases (N=22). Thirty subjects (39.0%) had a smoking history of at least 100 cigarettes in their lifetime. Myeloablative conditioning with total body irradiation was the most common pretransplant conditioning regimen. Sixty-one patients (85.0%) had active oral chronic graft-versus-host disease (cGVHD) within 1 year of OSCC/OED diagnosis. Immunosuppressant therapy for cGVHD was used in over 85.0% of the study cohort. The mortality risk post-alloHCT was significantly increased among patients who developed OSCC compared to those who did not (Hazard Ratio = 3.11; 95% CI, 2.34 – 4.13, $p<0.0001$). The 5-year survival rate of our study cohort was 61.0% (95% CI: 49.0-71.0). We identified a co-occurrence of other posttransplant head and neck cancers, particularly SCCs and basal cell carcinomas of the head and neck.

Conclusions: The median time from alloHCT to OSCC diagnosis was consistent with previously reported literature, though findings were notable for 12 cases diagnosed less than 4 years post-

alloHCT. The ventrolateral tongue was the most common site of secondary OSCC; however, a relatively high number of cases were identified at anatomic locations less common in the general population. The present data highlight the need for ongoing long-term monitoring of alloHCT patients along with careful oral screening.

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DEDICATION

This work is devotedly dedicated to my beloved husband, Ammar, who has been my backbone; I will forever appreciate all you have done,

to my precious two little boys, Ali and Yusuf,

and to my loving and always inspiring parents, Sawsan and Atif.

CHAPTER 1. BACKGROUND

1.1 Introduction

Hematopoietic cell transplantation (HCT) is a potentially lifesaving and life-extending therapy used to treat various conditions, including leukemias, myelodysplastic and myeloproliferative syndromes, hemoglobinopathies, and congenital metabolic defects. More than 25,000 transplants are performed annually in the United States.[1] Despite high success rates, allogeneic HCT (alloHCT) is associated with highly impactful acute morbidities, including veno-occlusive disease of the liver, acute graft-vs-host disease (aGVHD), and infections, which may be life-threatening. Long-term alloHCT survivors are also at risk for chronic posttransplant complications, most notably chronic GVHD (cGVHD), which remains a significant obstacle to transplant success.[2] Improved survival rates have also been associated with a greater incidence of secondary posttransplant malignancy. Incidence of secondary malignant neoplasms escalates as the duration of survival increases (incidence: 2–6% at ten years, and 6–13% at 15 years).[3–6] The most common secondary malignancies following alloHCT are hematologic malignancies, lymphoproliferative disorders, and solid malignancies.[7] Among solid secondary malignancies, melanomas, squamous cell carcinomas (SCC) of the skin and mouth, esophageal carcinoma, glioblastoma, and sarcomas are the most frequent, though incidence is lower than hematopoietic malignancies.[7–9] Inamoto et al. (2015) reported oropharyngeal squamous cell carcinoma (OPSCC) as the most common solid malignancy following HCT, with an incidence rate ranging from 32 to 92 per 100,000 person-years with a 7–16-fold higher risk than the general population.[4,10–13] Monitoring for oral and oropharyngeal malignancies is critical in alloHCT survivors; the National Institutes of Health recommends annual oral examinations for all patients surviving beyond one year.[14] Other groups support more frequent oral examination, particularly in patients

with oral cGVHD, analogous to follow-up in patients with other oral premalignant disorders.[4,12,15,16] Establishing long-term monitoring is essential as the risk for posttransplant malignancies, including oral cancers, increases over time.[4,12,15,16]

1.2 Incidence of secondary cancers post-alloHCT

Incidence of secondary cancers in patients following both autologous and alloHCT increase with time and vary by organ system.[17] Greater risks for secondary cancers of the skin, thyroid, oral cavity, esophagus, liver, brain/nervous system, bone, and connective tissues were identified after HCT when compared with the general population.[4,10–13,17]

Inamoto et al. (2015) provided an expert review of evidence-based cancer screening guidelines that can be applied to the HCT population.[4] The paper also described secondary cancer incidence and risk factors post-HCT. Oral and oropharyngeal cancers were the most frequent secondary cancer, with a standardized incidence ratio (SIR) ranging from 7.0 to 16 and an overall incidence of 32 to 92 cases per 100,000 person-years. Incidence of oral/oropharyngeal cancer also increased over time with 130-290 cases per 100,000 person-years at greater than ten years posttransplant.

Another study conducted by Yokota et al. (2011) concluded that the incidence and risk factors of secondary solid malignancies in Japanese alloHCT recipients are comparable to those reported in Western countries. Twenty-eight patients who developed 30 solid malignancies were identified within a median of 5.6 years after transplantation (range 0.3–17.6 years). The risk for developing malignancies was 2.16-fold higher than that of the age- and sex-adjusted in the general population. The cumulative incidence of solid malignancies at ten years after alloHCT was 2.4%. The risk was significantly higher for skin, oral cavity, and esophagus tumors. Despite being the most prevalent neoplasms in the Japanese population, no increase in gastric, colon, or lung

cancer was observed.[9] A cohort study by Atsuta et al. (2016) identified 269 secondary solid cancers in subjects treated with alloHCT. The cumulative incidence of secondary solid malignancy was 0.7% at 5 years and 1.7% at ten years after transplant. The risk was significantly higher than that in the general population for oral, esophageal, colon, skin, and brain/nervous system cancers.[13]

1.3 OSCC post-alloHCT

Oral cancer accounts for 2%–4% of all cancer worldwide, with oral squamous cell carcinoma (OSCC) representing greater than 90% of all oral cancers.14 Between 2004 and 2009, over 300,000 new cases of oral and oropharyngeal cancers were diagnosed worldwide. Though numerous studies have reported OSCC to be among the most common secondary neoplasms post-alloHCT, few studies have described the clinical features of OSCC in the HCT population.[4,8,9,12,13,15]

A recent multicenter cohort study comprehensively evaluated all patients diagnosed with oral malignancy or oral epithelial dysplasia (OED) following alloHCT.[5] Eighteen patients in their cohort were diagnosed with invasive carcinoma, 25 with OED, and 3 with verrucous hyperplasia. The average time between the first allogeneic transplant and diagnosis was 2 years for OED and 8 years for OSCC. Ninety-six percent of patients diagnosed with OED and OSCC also had a diagnosis of oral cGVHD. Smoking and alcohol use was common in the study cohort, with 42% of patients endorsing a history of smoking and 35% regularly consuming alcohol. OSCC mostly affected the tongue, followed by the buccal mucosa and lower lip. Half of OSCC cases were purely white, followed by red and white, and purely red lesions.[5] OED most commonly presented as isolated lesions on the lower lip. All OED presented as leukoplakia, erythroleukoplakia, or proliferative verrucous leukoplakia.

1.4 Risk factors for secondary solid malignancies post-allogeneic hematopoietic cell transplantation

Head and neck cancer is the sixth most common human cancer, and oral cancer constitutes 48% of these malignancies.[21] Tobacco, smokeless tobacco, alcohol consumption, and HPV are considered the major risk factors for the development of oral cancer in the general population.[21,22] Other noted risk factors include tissue inflammation and genetic susceptibility.[21] Risk factors for secondary solid malignancies following alloHCT have been examined by many researchers and include chemotherapy, total-body radiation (TBI), male gender, viral infection (e.g., EBV), age at transplant, cGVHD, and use of immunosuppressive therapy.[7]

GVHD warrants special consideration in cancer risk following alloHCT. cGVHD is characterized by a state of immunodeficiency, which is further intensified by prolonged immunosuppressive therapy to treat the disease.[23,24] Moreover, cGVHD shows features of autoimmunity and inflammation, both of which have been implicated in cancer risk.[25–27] The interaction between inflammation and immunosuppression in the development of OSCC is not fully understood but has been speculated to be related to altered tissue repair, which enhances the risk for tumor progression.[23] Furthermore, immunosuppressive therapy with antirejection agents such as azathioprine (AZA) is known to have carcinogenic effects and to be implicated in the development of malignancies following both solid organ transplantation and alloHCT.[3,23,28]

An international case-control study of 24,011 patients treated with alloHCT or syngeneic HCT at the Fred Hutchinson Cancer Research Center (FHCRC) revealed invasive or in situ solid cancers in 183 patients with a mean follow-up of 6 years post-HCT.[10] The presence of cGVHD and immunosuppressive therapy was strongly related to OSCC risk; however, there was no increased risk in non-squamous cell cancers. A 4.6x relative risk (RR) for SCC was seen in patients treated with immunosuppressive therapy for greater than 24 months. Development of cGVHD was also

the most important risk factor for nonskin SCC in a study by Baker et al. (2019).[3] Elevated risk was also seen in cGVHD patients requiring long-term immunosuppressive therapy.[4] A borderline significant 3-fold increase in OSCC risk was observed among patients given AZA and steroids without cyclosporine (CSP), but no increase in risk was found in those receiving CSP-based therapy with AZA, patients treated with steroids alone, or those treated with other therapies. cGVHD was also implicated in the development of posttransplant solid malignancy in a retrospective cohort study by Yokota et al. (2011). Multivariate analysis found cGVHD and primary diagnosis of malignant lymphoma to have RR of 2.4 and 4.7, respectively.[9] When the cohort was limited to secondary tumors in the oral cavity and esophagus, a much higher risk was seen in patients with malignant lymphoma as a primary disease (RR = 8.1).

Pre-transplant conditioning has also been associated with cancer risk.[3,26] Baker et al. (2019) retrospectively studied the impact of total body irradiation (TBI) dose and fractionation on the risk of secondary solid malignancies in the settings of non-myeloablative (NMC) and reduced-intensity conditioning (RIC) regimens.[3] The study revealed that 499 patients (11%) developed at least one secondary solid malignancy, occurring at a median of 10.3 years (range, 1.0-39.7 years) post-alloHCT. Another cohort study by Ringden et al. (2014) compared the risks of second solid cancers after RIC/NMC before HCT with patients treated with myeloablative conditioning (MAC) and with control subjects from the general population.[19] The cumulative incidence of second solid cancers for the entire cohort was 0.54 at 1 year, 1.69 at 5 years, and 3.35 at 10 years after transplantation. The authors concluded that patients treated with RIC/NMC must receive screening for solid cancers comparable to those treated with MAC.

The anti-infectious agent voriconazole has been associated with cancer risk in alloHCT recipients.[29] A retrospective cohort study of 381 adult patients completed by Wojenski et al. (2015) found cumulative days of voriconazole use to have a statistical association with the development of cutaneous SCC. [26] SCCs were identified in 26 of 312 patients treated with voriconazole compared to 1 out of 69 patients treated with alternative antifungal agents. The study estimated the cumulative incidence of SCC to be 19% at 5 years posttransplant in patients treated with voriconazole. Although the mechanism is uncertain, it has been proposed that the drug may cause photo-induced DNA damage.

1.5 Research aims

Our study aimed to evaluate patient demographics, characteristic features, clinical outcomes, and prevalence of OSCC risk factors in patients developing diagnosed with OSCC and/or OED post-alloHCT.

1.6 Research questions

1. What is the average time (in months/years) from alloHCT until the diagnosis of OSCC in our study cohort?
2. Are OSCCs identified at an earlier stage in our population than the general population in the United States?
3. What percentage of patients were treated with surgery (with or without neck dissection) vs. radiotherapy vs. chemotherapy vs. other therapies?
4. How does the 5-year survival rate in our cohort compare with the OSCC survival rate in patients who are transplant naïve?

5. What was the recurrence rate for OSCC in our population?
6. Lesion characteristics:
    a. What are the most common physical locations of OSCC and OED in our cohort?
    b. What percentage of subjects reported pain/sensitivity at the lesion site at the time of lesion diagnosis?
    c. Were antecedent lesions identified at the site of future OSCC development during posttransplant oral medicine (OM) examinations?
    d. What were the most common physical characteristics at the site of OSCC 1 and 2 years prior to diagnosis?
    e. Were symptoms present at the site during posttransplant OM examinations?

7. What was the average duration of immunosuppressive therapy in our cohort?
8. Did patients in our cohort have exposure to previously established OSCC risk factors?
    a. History of oral mucosal cGVHD.
    b. Tobacco use.
    c. Alcohol use.
    d. Use of high-dose TBI.
    e. Voriconazole.
    f. Aza (alone) or in combination with CSP or steroids.
    g. Advanced/ young age at transplant.

CHAPTER 2. MATERIALS AND METHODS

A retrospective chart review was completed to examine the clinical characteristics of patients treated with allogeneic hematopoietic cell transplantation (alloHCT) at Fred Hutchinson Cancer Research Center (FHCRC)/Seattle Cancer Care Alliance (SCCA) (Seattle, WA) between 1969 and 2018. Cases of oral squamous cell carcinoma (OSCC) and oral epithelial dysplasia (OED) were identified through the Gateway database. The Gateway database contains transplant data from the 1960s to the present day and is used in both clinical patient care and research workflows. Patient data supports all four Consortium partners: FHCRC, SCCA, University of Washington (UW) Medicine, and Seattle Children's Hospital. We utilized FHCRC's Optical Web Library (OWL) (Seattle, WA) to obtain details related to demographics, smoking and alcohol history, primary disease, conditioning therapy, graft-versus-host disease (GVHD) status, immunosuppressive therapy, and 5-year survival post-OSCC diagnosis via Long-term Follow-up survivorship databases and clinical notes. The presence or absence of oral symptoms and oral lesion characteristics at the site of OSCC/OED diagnosis were obtained via chart note review in OWL and electronic medical records (EMRs) via Epic Hyperspace (Verona, WI).

The following search terms were used to identify potential subjects in Gateway: "Carcinoma", "Dysplasia", "Cheek," "Gum," "Lips," "Mouth," "Oral," "Tongue," and "Tonsil." Subjects were categorized by unique patient numbers. EMRs were queried using the following search terms to identify data of interest: "Carcinoma," "Squamous," "Dysplasia," "Oral Cancer," "Radiation," "Neck dissection," "Ulcer(ation)," "Oral medicine," "Otolaryngology," "Biopsy," "Erythroplakia," "Leukoplakia".

The study was approved through the FHCRC Institutional Review Board (IRB) under protocol #999.209 (Study Title: Master Protocol for Collection of Clinical Data and Storage of Leftover

Specimens from Patients Treated at SCCA and FHCRC. Principal Investigator: Stephanie Lee, MD) and through the UW Human Subjects Division (IRB) ID: STUDY00013750).

Inclusion criteria

- Patients who were treated with alloHCT for the treatment of malignant or non-malignant disease at SCCA/FHCRC between 1969 and 2018
- Survival for at least 12 months posttransplant
- OSCC/OED confirmation in the patient's EMR (e.g., pathology report, clinical progress note, surgical note, etc.)

Exclusion criteria

- AlloHCT for nonhematologic solid malignancies
- Prior diagnosis of dyskeratosis congenita, Fanconi anemia, or other DNA repair disorder

Data variables

1. Demographics (Age, gender, race, and ethnicity)
2. Smoking history (History of cigarette smoking, smoking history of at least 100 cigarettes in entire life, time since the last period of regular tobacco use)
3. Smokeless tobacco use (Never, daily, occasional, unknown) + duration of use
4. Alcohol history (Non-drinker, current drinker) + (number of drinks per day/week/month when available)
5. Clinical indication for alloHCT (Primary disease).
6. History of other head and neck cancer

7. Transplant history (Date of transplant, age at transplant, donor type, graft source, history of donor lymphocyte infusion)
8. Conditioning regimen (MAC, NMA/RIC), Radiation dose (Low-dose TBI, single-fraction TBI, fractionated TBI, high-dose fractionated TBI)
9. GVHD prophylaxis
10. GVHD characteristics (History of aGVHD, History of cGVHD, cGVHD severity score (global), oral cGVHD severity score, type(s) of systemic immunosuppression, duration of systemic immunosuppression, type of oral cGVHD therapy)
11. Clinical features of SCCA/OED (Time from transplant to diagnosis of SCCA/OED, clinical TNM stage of OSCC, histologic grade of OED, lesion site, lesion characteristics, and reported symptoms were collected at the time of diagnosis, 1 year, and 2 years prior to diagnosis where available)
12. Treatment of OSCC/OED lesion (Surgical excision only, surgical excision with neck dissection, surgical excision with radiation therapy, surgical excision with neck dissection, radiation therapy, and chemotherapy, laser)
13. 5-year survival post-OSCC diagnosis
14. Lesion recurrence

Statistical analysis

Study data were collected and managed using Research Electronic Data Capture (RedCap) electronic data capture tools hosted at the University of Washington.[30,31] Descriptive statistics were used to summarize the general characteristics of the data variables. Overall survival was calculated from the date of diagnosis of OSCC to the date of death. The risk of mortality was

calculated by treating OSCC as a time-dependent covariate adjusting for patient age, type of donor (cord vs. matched unrelated vs. mismatched unrelated vs. matched related vs. mismatched related vs. haploidentical), and severity of disease (categorized as low vs. intermediate vs. high). All statistical analyses were performed using Microsoft Excel Version 16.63.1. and SAS version 9.4.

CHAPTER 3. RESULTS

Patient and transplant characteristics

Eighty-four cases of oral squamous cell carcinoma (OSCC) and 10 cases of oral epithelial dysplasia (OED) were identified in 78 subjects. The median age at the time of transplant was 37.8 years (range 8.0-67.0). Most of our study cohort were males (71.8%). The most common indication for alloHCT was chronic myeloid leukemia (CML), followed by acute myeloid leukemia (AML). The donor type was matched related (55.1%) followed by matched unrelated (29.5%). Patient demographics and transplant-specific data are summarized in Table *1*.
The average time from alloHCT to the diagnosis of OSCC/OED was 13 years (median 12.3 years, range 0.8-30.0 years) *(Figure 1).* Twelve cases of OSCC were diagnosed less than 4 years posttransplant (Figure *2*).

Fifty-five subjects (70.5%) of the study cohort survived beyond 5 years post-OSCC/OED diagnosis. Overall survival rates post OSCC diagnosis at 5 years were 61.0% (49.0-71.0%), 46.0% (34.0-57.0%) at 10 years, 37.0% (25.0-49.0%) at 15 years, and 24.0% (13.0-38.0%) at 20 years (Figure 3). The risk of death post-alloHCT is significantly increased among our patients who developed OSCC compared to those who did not (Hazard Ratio = 3.11; 95% CI, 2.34 – 4.13, $p<0.0001$).

Clinical features of OSCC and OED

OSCC lesions were frequently observed on the ventrolateral surface of the tongue (N=23, 27.7%), followed by the vermilion border of the lips (N=14, 16.9%) and the buccal mucosa

(N=10, 12.0%) (Figure *4*). Lesions were observed more frequently on the left side of the oral cavity (N=37, 39.3%) than on the right side (N=28, 29.7%). Same-site lesion recurrence was documented in 23.4% of the cases, with 22 subjects developing second primary tumors. OSCC cases presented as ulceration (N=25, 29.7%), leukoplakia (N=16, 19.0%), exophytic masses (N=11, 13.0%), mixed red/white lesions (N=3, 3.5%), and erythroplakia (N=2, 2.3%) (Table 2). Pain and/or sensitivity were present at the lesion site in 27 cases (32.0%). Clinical at 1 year and 2 years before OSCC diagnosis are summarized in Table *3*.

Among 10 OED cases, 5 presented on the tongue, 2 on the gingiva, 2 on the palate, and 1 on the labial mucosa (Table *4*). All lesions were described as leukoplakia or ulceration. The histologic grade of OED was high-grade in 6 cases (i.e., moderate-to-severe or higher) and mild in 4 cases (i.e., mild-to-moderate or lower). Three OED cases transformed into OSCC. Data related to OSCC TNM staging was available for 27 subjects; the majority were at stage 1 (T1N0M0) at the time of diagnosis (N=17) (Table *5*). Most lesions were treated by surgical excision only (55.0%) or surgical excision with neck dissection (18.0%). The management of cases is summarized in *Figure 5.*

OSCC/OED Risk Factors

The presence or absence of transplant-specific OSCC risk factors is summarized in Table *6*. Myeloablative conditioning with total body irradiation was the most frequent conditioning regimen (57.7%). Cyclophosphamide and busulfan were the most common chemotherapy agents used in pretransplant conditioning. Thirteen subjects (17.3%) had a documented use of

azathioprine combined with steroids and/or cyclosporine as part of their immunosuppressive regimen (**Error! Reference source not found.**). Six patients (7.7%) had documented exposure t o voriconazole.

Thirty subjects (38.5%) had a smoking history of at least 100 cigarettes in their lifetime. Alcohol consumption data were available for 61 subjects, of which 15 were frequent alcohol consumers. Details related to smoking and alcohol consumption are summarized in Table *7*.

Sixty-one patients (87.2%) had active oral chronic graft-versus-host disease (cGVHD) within 1 year of OSCC/OED diagnosis. Patients in our cohort also had documented cGVHD in other organ systems, including the: skin (75.0%), eyes (49.0%), liver (38.0%), gastrointestinal tract (35.0%), lungs (19.0%), joints and fascia (14.0%), and genitalia (13.0%) (Figure *7*). Prior history of head and neck cancer was documented in 22 cases with OSCC (Table *8*).

Table 1. Patient Characteristics and Donor Type

N	78
Age at transplant, median (range) years	37.8 (8.0-67.0)
	N (%)
Gender	
Male	56 (71.8)
Female	22 (28.2)
Race	
White/Caucasian	69 (88.5)
Black/African American	1 (1.3)
Asian	3 (3.8)
Native Hawaiian or Other Pacific Islander	1 (1.3)
Other	4 (5.1)
Primary disease	
CML	27 (34.6)
AML	13 (16.7)
AA	9 (11.5)
MDS	8 (10.3)
ALL	6 (7.7)
NLL	4 (5.1)
CLL	3 (3.8)
NHL	2 (2.6)
Malignant lymphoma	2 (2.6)
AEL	1 (1.3)
Myelofibrosis	1 (1.3)
HL	1 (1.3)
AMML	1 (1.3)
Donor type	
Matched, Related	43 (55.1)
Matched, Unrelated	23 (29.5)
Mismatched, Related	6 (7.7)
Mismatched, Unrelated	3 (3.8)
Missing	3 (3.8)

AEL = Acute erythroleukemia; ALL = Acute lymphocytic leukemia; AML = Acute myeloid leukemia; AMML = Acute myelomonocytic leukemia; AA = Aplastic anemia; CLL = Chronic lymphocytic leukemia; CML = Chronic myeloid leukemia; HL = Hodgkin lymphoma; MDS = Myelodysplastic syndrome; NHL = non-Hodgkin lymphoma; NLL = non-lymphocytic leukemia.

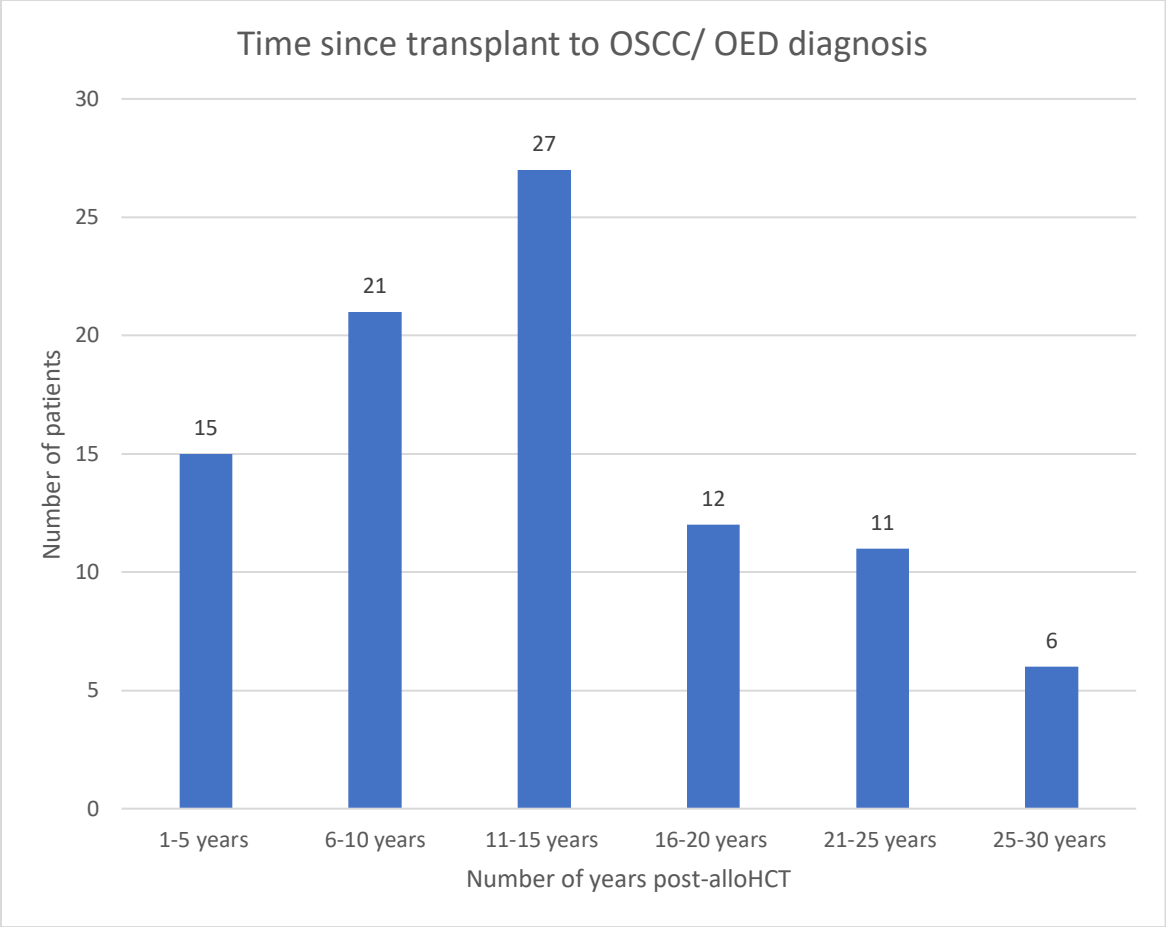

Figure 1. Time since transplant to each OSCC/OED diagnosis

alloHCT = Allogeneic hematopoietic cell transplantation; OED = Oral epithelial dysplasia; OSCC = Oral squamous cell carcinoma.

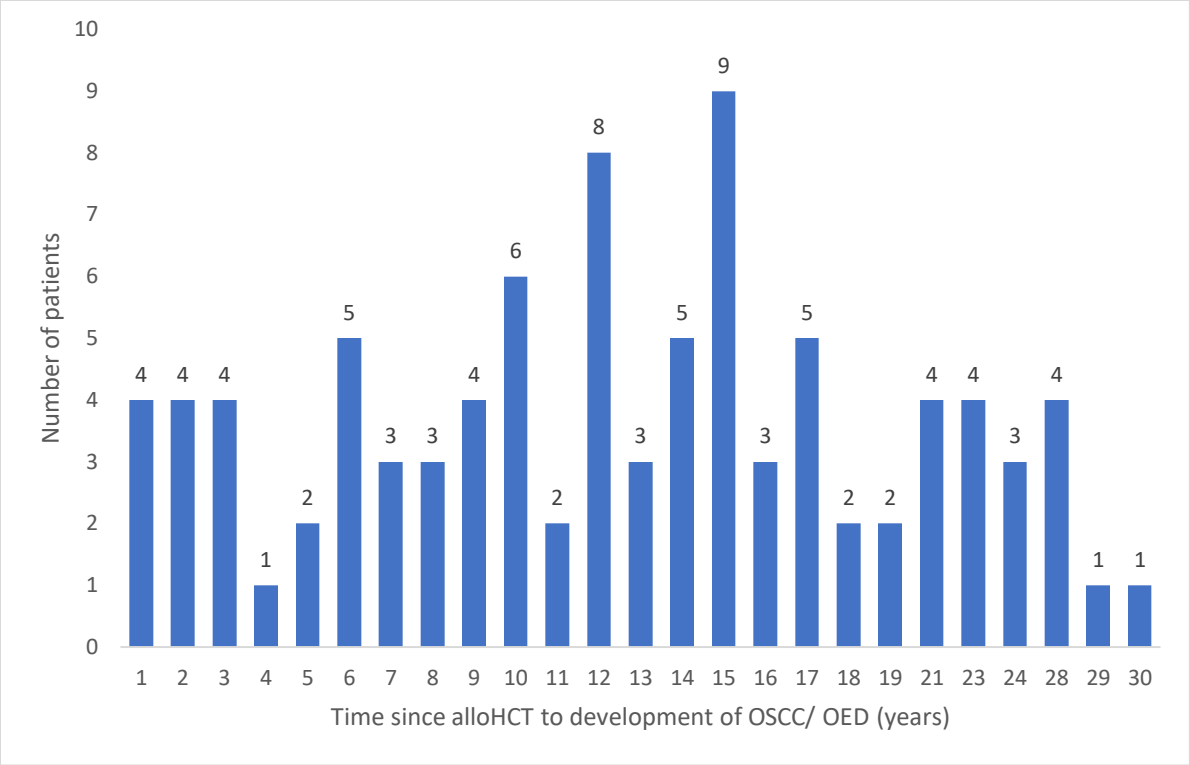

Figure 2. Time since transplant to each OSCC/ OED diagnosis by year

alloHCT = Allogeneic hematopoietic cell transplantation; OED = Oral epithelial dysplasia; OSCC = Oral squamous cell carcinoma.

Table 2. OSCC lesion characteristics

Clinical Appearance	**N (%)**
Ulceration	25 (29.7)
Leukoplakia	16 (19.0)
Exophytic mass	11 (13.0)
Mixed red/white lesions	3 (3.5)
Erythroplakia	2 (2.3)
Unknown	27 (32.1)

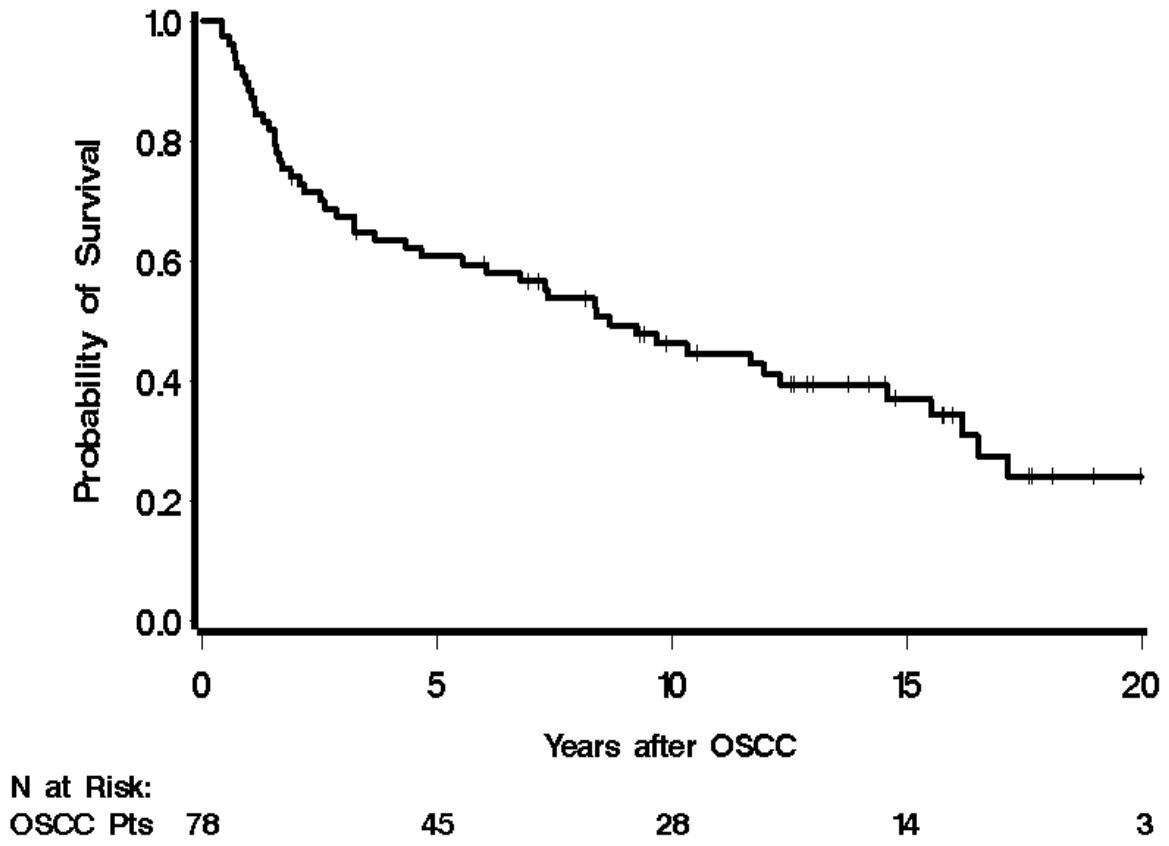

Figure 3. Kaplan–Meier curve of overall survival rate for patients who developed OSCC post-alloHCT.

Curves are calculated from the time of diagnosis of OSCC to the death date.

Point estimates of survival rate at various timepoints (with 95% confidence intervals): 5 years, 61% (49-71%),10 years, 46% (34-57%), 15 years, 37% (25-49%), 20 years, 24% (13-38%).

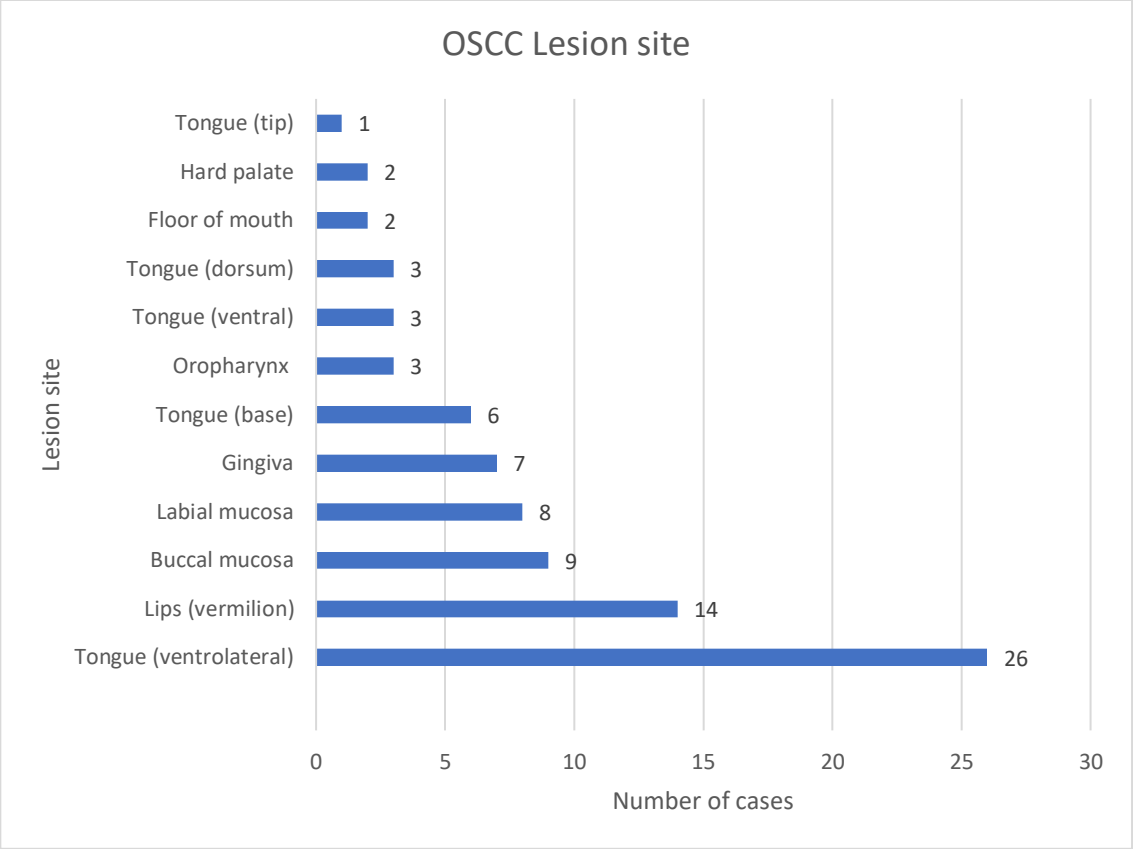

Figure 4. OSCC lesion sites

Table 3. Lesion characteristics at 1 and 2 years before biopsy

Lesion characteristics at 1 year			
Leukoplakia	Erythema/Atrophy	Ulceration	Total
10	7	5	22
Lesion characteristics at 2 years			
Leukoplakia	Erythema/Atrophy	Ulceration	Total
6	3	2	11

Table 4. OED lesion characteristics

Median time from transplant to diagnosis in years (range)	19.5 (9.0-31.6)
	N (%)
OED histological grade	
High grade	6 (60.0%)
Low grade	4 (40.0%)
Site	
Tongue	5 (50.0%)
Gingiva	2 (20.0%)
Labial mucosa	1 (10.0%)
Hard palate	1 (10.0%)
Soft palate	1 (10.0%)
Clinical description	
Leukoplakia	6 (60.0%)
Ulceration	3 (30.0%)
Unknown	1 (10.0%)
Pain/ Sensitivity	3 (30.0%)
Post-treatment recurrence	4 (40.0%)
Transformation to OSCC	3 (30.0%)

Abbreviations: OED = Oral epithelial dysplasia; OSCC = Oral squamous cell carcinoma.

Table 5. TNM Staging

TNM stage	**N (%)**
T1N0M0	17 (21.8)
T2N0M0	6 (7.7)
T2N2b	1 (1.3)
T1N2cMx	1 (1.3)
T4aN0M0	1 (1.3)
T4N2cM2	1 (1.3)
Unknown stage	51 (65.4)
Abbreviations: T = Tumor; N = Nodal metastasis; M = Distant metastasis	

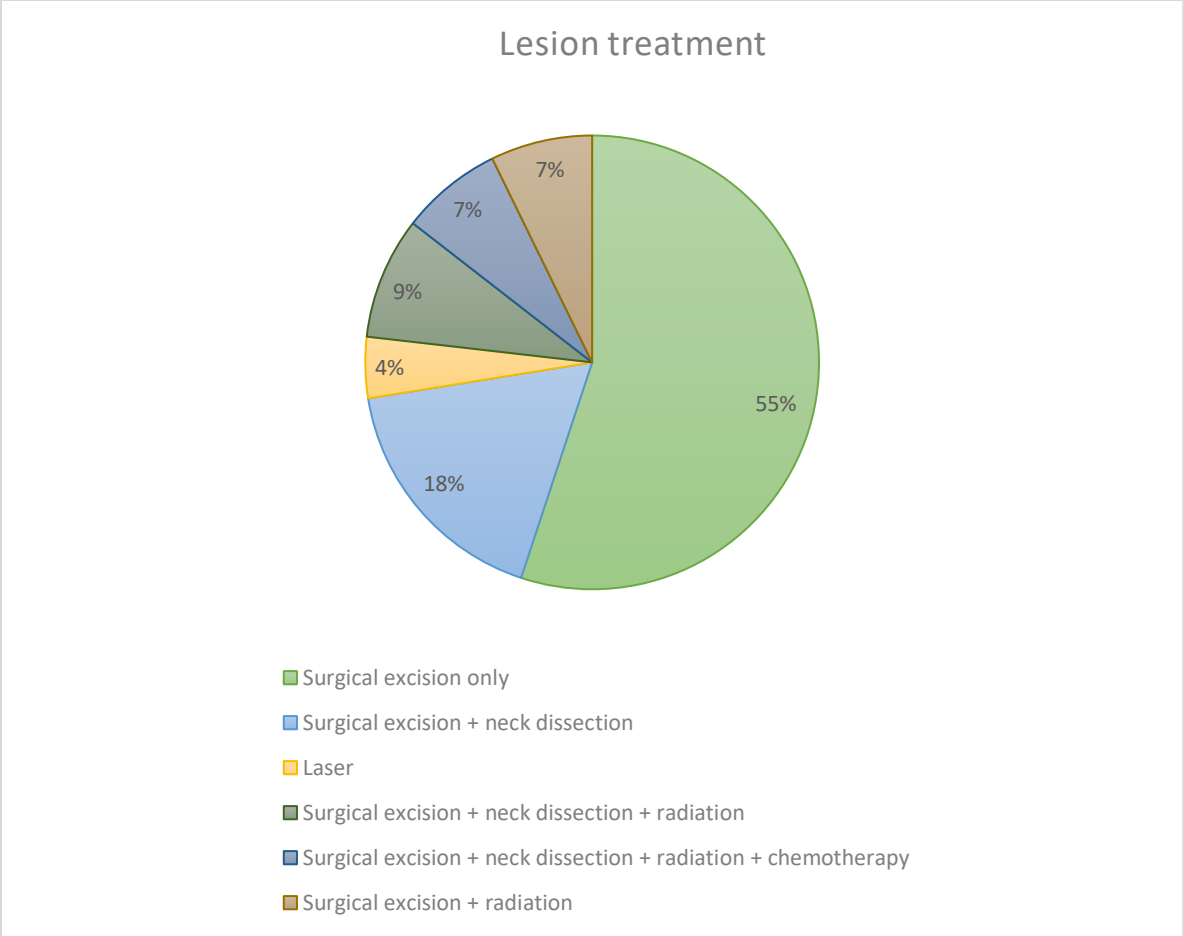

Figure 5. OSCC and OED lesion treatment

OED = Oral epithelial dysplasia; OSCC = Oral squamous cell carcinoma.

Table 6. OSCC Risk Factors

Conditioning regimen	N (%)
Myeloablative conditioning with TBI	45 (57.7)
Myeloablative conditioning without TBI	20 (25.6)
Non-myeloablative conditioning with TBI	3 (3.8)
Non-myeloablative conditioning without TBI	7 (9.0)
Missing	3 (3.8)
Chemotherapy	
Cyclophosphamide	48 (61.5)
Cyclophosphamide + Busulfan	14 (17.9)
Fludarabine	4 (5.1)
Fludarabine + Treosulfan	3 (3.8)
Cyclophosphamide + Anti-thymocyte globulin	3 (3.8)
Busulfan)	2 (2.6)
Cyclophosphamide + Busulfan, + Imatinib	2 (2.6)
Busulfan + Thiopeta + Melphalan	1 (1.3)
Carmustine + Chlormethine	1 (1.3)
TBI	
Fractionated TBI (600-1200 cGy or 1200-1400 cGy)	23 (29.5)
High-dose fractionated-TBI (1440-1750 cGy)	20 (25.6)
Low-dose TBI (200-450 cGy given in 1 or 2 fractions)	6 (7.7)
Single-fraction TBI (600-1000 cGy)	4 (5.0)
N/A	25 (32.1)
GVHD prophylaxis	
Methotrexate + Cyclosporine	51 (65.4)
Methotrexate only	7 (9.0)
Methotrexate + Tacrolimus	5 (6.4)
Cyclosporine + Azathioprine	1 (1.3)
Tacrolimus only	1 (1.3)
Tacrolimus + Mycophenolate mofetil	1 (1.3)
Other	12 (15.4)
Voriconazole use	6 (7.7)
History of acute GVHD	61 (78.2)
History of chronic GVHD	72 (92.3)
Systemic chronic GVHD treatment*	
Prednisone	64 (85.3)
Cyclosporine	46 (61.3)

Table 6. OSCC Risk Factors (Cont'd)	
Tacrolimus	18 (24.0)
Azathioprine	13 (17.3)
Methotrexate	12 (16.0)
Mycophenolate mofetil	8 (10.7)
Sirolimus	2 (2.7)
Rituximab	2 (2.7)
Thalidomide	1 (1.3)
Other	14 (18.7)

TBI = Total body irradiation; GVHD = Graft-versus-host disease; CGy = Centi-gray

*Multiple treatments per patient are possible, so the frequencies do not sum to N = 78, and the percentages do not sum to 100%.

Table 7. Smoking and Alcohol History

Smoking history	**N (%)**
Never	41 (52.5)
Daily	25 (32.1)
Occasional	6 (7.7)
Unknown	6 (7.7)
Smoking history of at least 100 cigarettes in life	
Yes	30 (38.5)
No	42 (53.8)
Unknown	6 (7.7)
History of chewing tobacco or snuff	
Yes	4 (5.1)
No	68 (87.2)
Unknown	6 (7.7)
Time since last period of regular tobacco use	
Within the past month	6 (7.7)
Within the past 5 years	2 (2.6)
Within the past 10 years	3 (3.8)
10 years or more	20 (25.6)
Never smoked regularly	40 (51.0)
Unspecified	7 (9.0)
Alcohol history	
Never	15 (19.2)
Occasional	31 (39.7)
4 or more times a week	15 (19.2)
Unspecified	17 (21.8)

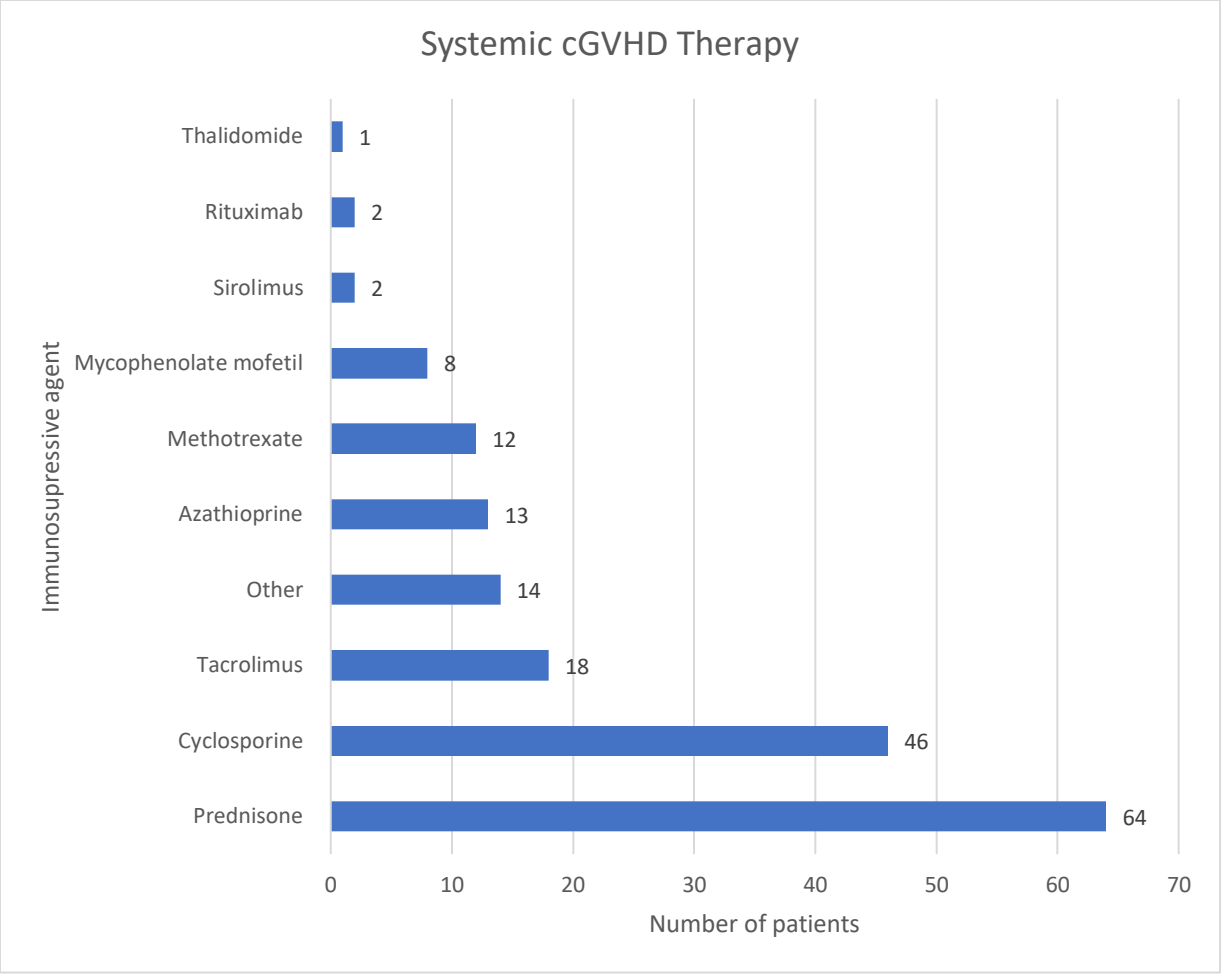

Figure 6. Systemic cGVHD therapy

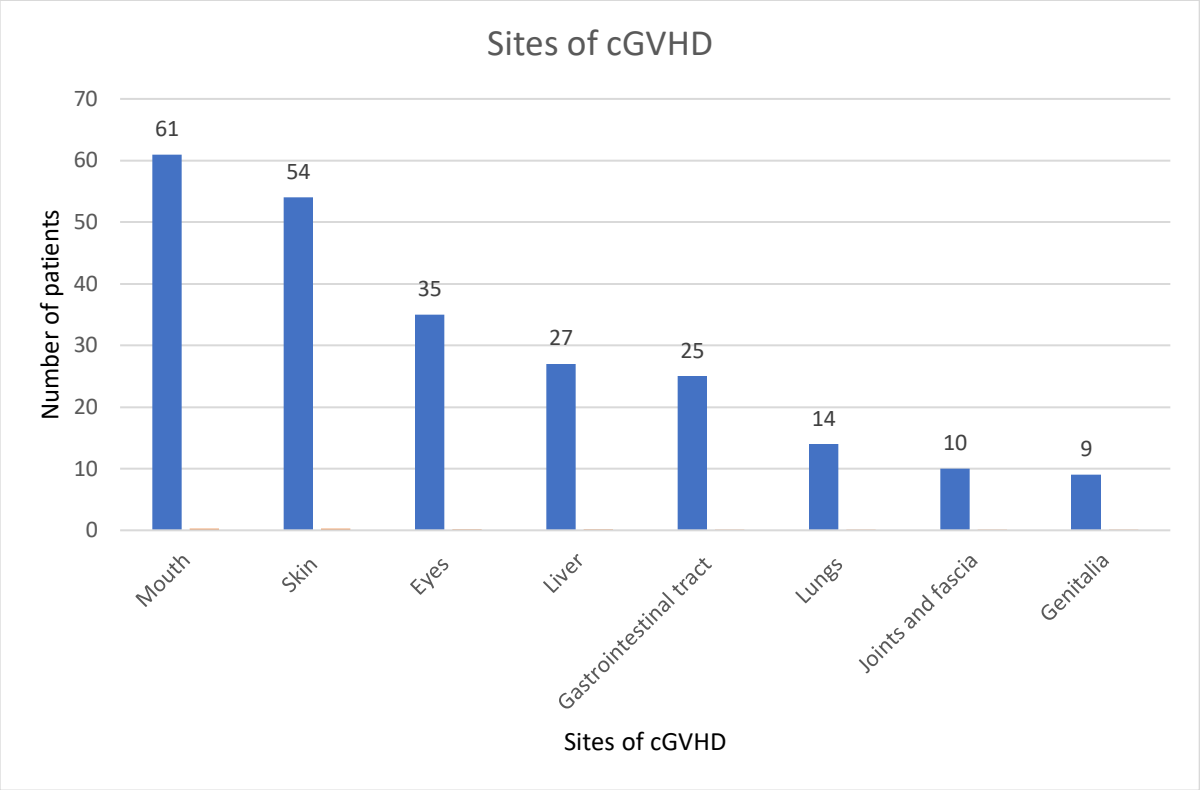

Figure 7. Sites of cGVHD

Table 8. Previous history of secondary head and neck cancers

Location	Type of cancer	N
Face	Basal cell carcinoma	13
	Squamous cell carcinoma	6
Head/Scalp	Squamous cell carcinoma	2
Thyroid	Papillary carcinoma	1
Total		22

CHAPTER 4. DISCUSSION

Improved survival after allogeneic hematopoietic cell transplantation (alloHCT) is associated with a greater incidence of secondary posttransplant malignancies, including oral cancers. [3–6] Though oral cancers are among the most common secondary solid malignancies posttransplant; few studies have evaluated the patient demographics, characteristic features, clinical outcomes, and prevalence of oral squamous cell carcinoma (OSCC) and oral epithelial dysplasia (OED) risk factors post-alloHCT.[5,6,17,20,32,33]

Time to diagnosis of OSCC has been variably reported in the alloHCT population.[5,34] The median time from alloHCT to the diagnosis of OSCC/OED in our study cohort was 12.3 years (range 0.8-30.0 years). Gallagher et al. (2007) identified 28 patients who developed 30 solid malignancies at a median of 6.8 years after alloHCT.[34] Four cases of OSCC were present in the cohort diagnosed at a median of 9 years posttransplant. A similar median time was observed in a study by Mawardi et al. (2011).[5] Eighteen cases of invasive OSCC were diagnosed at a median time of 8 years (range 1-14 years) post-alloHCT. OSCC cases are infrequently reported within the first few years posttransplant. Our study identified 13 cases of OSCC that developed within the first 4 years post-alloHCT. Kruse et al. (2009) reported 8 of 30 oral carcinomas diagnosed between 1 and 4 years posttransplant in a cohort of alloHCT patients treated over a 30-year period in Switzerland.[32] A Japanese study published by Tanaka et al. (2017) reported 4 secondary oral carcinomas within the first 5 years posttransplant in a population treated between 1982 and 2012. [35]

In our cohort, 72% of 78 patients diagnosed with OSCC/OED were male, which is slightly higher than the relative prevalence of OSCC in the general US population, in which the male to female ratio is slightly more than 2:1.[36] The median age at the time of alloHCT was 37.8 years

(range 8.0-67.0). The influence of age on secondary cancer development has been variably reported in other studies.[3,13,37] Atsuta et al. (2014) determined older age at transplant to be a significant risk factor for the development of OSCC, while Baker et al. (2019) found that younger age at transplant was an important risk factor.[3,13] Majhail et al. (2011) identified older age (>50 years) as an independent risk factor for secondary solid cancers;[37;] however, the same study also noted a trend toward increased risks of second cancers among younger patients (<35 years, O/E 1.74, p=0.09).[37] Among our cohort, only 25% were over the age of 50 at the time of alloHCT. Questions remain on the true impact of age at transplant on the development of OSCC post-alloHCT; therefore, future studies are required with sufficient age distribution to allow for analysis.

Though cancer staging details were not available for all patients in our cohort, available data suggested an earlier stage at diagnosis in the alloHCT population when compared to the general US population. Among 27 patients with available data, 23 patients were diagnosed with stage 1 or stage 2 cancers (N=17 and N=6, respectively). In the US population, approximately 28% of oral and oropharyngeal cancers are diagnosed at an early stage.[38] Early stage at diagnosis was also suggested by the relative frequency of OSCC therapies, with 55% of cases managed with surgical excision alone and an additional 18% treated with surgical excision and neck dissection without therapeutic radiation. We hypothesize that early detection in our cohort is most likely related to regular monitoring for oral cancers in the alloHCT population.[39]

Though cancers were more frequently diagnosed at an early stage, the 5-year survival in our cohort was 61.0% (95% CI: 49.0-71.0) which is lower than the 68% (95% CI: 67.5 – 68.5) 5-year survival rate for oral and oropharyngeal squamous cell carcinoma (OPSCC) in the general population reported by the National Cancer Institute's Surveillance, Epidemiology, and End

Results (SEER) program between 2012-2018.[40] This finding is most likely due to the presence of other comorbidities within the alloHCT population as prior studies have confirmed higher mortality rate in transplant survivors when compared to those who are transplant naïve, including a 4- to 9-fold higher mortality rate in 5-year relapse-free survivors when analyzed for a minimum of 30 years. [41] The excess mortality rate among HCT recipients translates to an estimated 30% lower life expectancy than that of the general US population, irrespective of the current age. The major causes of excess deaths described by a study by Martin et al. (2010) include recurrent disease, secondary malignancies, infections, cGVHD, respiratory diseases, and cardiovascular diseases.[41] Given that SEER statistics group OSCC and OPSCC cases together, the lower 5-year survival in our cohort may also be influenced by the low number of OPSCC cases in our cohort (N = 3), as OPSCC is estimated to have an approximately 85% 5-year survival rate in the general population.[38] Furthermore, after adjusting for covariates, the risk of death was increased in alloHCT patients developing OSCC when compared to those who did not (Hazard Ratio = 3.11; 95% CI, 2.34 – 4.13, $p<0.0001$), further highlighting the need for long-term monitoring in this population, particularly those with other OSCC risk factors.

In our study cohort, OSCC lesions were frequently observed on the ventrolateral surface of the tongue (N=23), followed by the buccal mucosa (N=10), and the labial mucosa (N=8), and the gingiva (N=7). Similar findings were observed by Mawardi et al. (2011) in which the tongue was the most common site (N=10; 56.0%), followed by buccal mucosa (N=7; 39.0%).[5] With the exception of the tongue, these sites are not considered high-risk locations in patients who are transplant naive. [36,42] Furthermore, only 2 cases of OSCC in our population affected the floor of the mouth, the second most common site for OSCC in the western populations.[36,42]

It seems probable that the differences in lesion locations are related to the impact of oral mucosal cGVHD. Oral cGVHD most commonly affects the tongue and the buccal mucosa and is regarded as a significant risk factor for secondary OSCC.[17,20,43] In a recent systematic review by Majeranowska et al. (2022), oral cGVHD preceded OSCC lesion development in 65.4% of alloHCT patients.[44] In their systematic review, the two common locations for OSCC occurrence post-alloHCT were also the tongue (28.2%) and the buccal mucosa (10.6%). Oral cGVHD was prevalent among our study cohort. Sixty-one patients (84.7%) had active oral cGVHD within 1 year of OSCC/OED diagnosis.

Another notable finding in our cohort was the presence of clinically appreciable oral lesions at the future site of OSCC development at 1 and 2 years prior to diagnosis. For example, "leukoplakia" was present for at least 1 year prior to diagnosis in 16 OSCC cases. The lack of biopsy data at earlier time points limits the conclusions that can be drawn from this finding, though it is possible that OED or emerging OSCC was present a considerable time prior to biopsy-confirmed diagnosis. Posttransplant surveillance should occur regularly in all alloHCT patients and oral biopsies, or repeat biopsies, should be considered whenever malignancy is suspected.[16] Given the complexities in differentiating oral cGVHD and other oral mucosal lesions from OED/early OSCC, it would be valuable to characterize the relative use, or lack of use, of monitoring and adjunctive diagnostic agents such as oral photography, toluidine blue testing, autofluorescence visualization, chemiluminescence, and oral cytology in future studies.

One final interesting observation was the diagnosis of other secondary head and neck cancers diagnosed in patients developing OSCC posttransplant. Twenty-two patients (28.0%) in our OSCC cohort were diagnosed with secondary basal cell carcinoma or cutaneous SCC presenting in the head and neck region. This relatively common co-occurrence has not been previously

described in the literature; however, findings in additional studies designed to evaluate the statistical association are warranted to confirm the association. In either case, it is recommended that clinicians remain vigilant for other head and neck cancers during follow-up evaluations.

Conclusions drawn from our study must be considered within the context of the general limitations of all retrospective studies. First, not all data variables were available for each of our study subjects. Details of cancer staging, lesion characteristics, chronic GVHD therapy doses and scores, and topical oral cGVHD treatments were missing for many patients. There may also have been a lack of uniformity in clinical documentation, especially in the description of oral lesions when described by medical rather than dental specialists. Furthermore, study participants were mostly Caucasian, which impacts the generalizability of the findings to people of other races. Lastly, a control group of non-OSCC/OED patients would be required to assess risk factors for OSCC/OED development; however, due to limitations related to data availability, we elected to analyze only alloHCT patients with documented OSCC/OED in this initial study. In the future, retrospective matched case-control studies or prospective cohort studies with comparison groups should be performed to further characterize risk factors for OSCC/OED development.

This study represents one of the largest cohorts of OSCC cases ever evaluated in HCT literature. Strengths of our study include a nearly 50-year treatment period during which OSCC/OED could be identified. Our center also includes one of the few Oral Medicine services in the country that is fully integrated with the HCT and Long-term follow-up (survivorship) services allowing for expert assessment and monitoring of posttransplant oral lesions.

Conclusions

In summary, the current study evaluates a large number of OSCC and OED cases post-alloHCT over a study period of nearly 50 years. The median time to posttransplant OSCC diagnosis was consistent with previously reported literature; however, findings were remarkable for 12 cases diagnosed within less than 4 years posttransplant. The mortality risk is increased post-alloHCT in patients diagnosed with OSCC compared to non-OSCC transplant patients. Additionally, the 5-year survival rate of OSCC cases is lower than that of the general population, consistent with relative life expectancy in the alloHCT population. The clinical locations of OSCC and OED included areas both common (e.g., ventrolateral tongue) and uncommon (e.g., buccal mucosa) to the general OSCC population. We identified a co-occurrence of other secondary head and neck cancers prior to OSCC/OED diagnosis, particularly cutaneous SCCs and BCCs presented in the head and neck region. Our study provided critical information that benefits clinicians when caring for and counseling patients about screening and prevention of secondary OSCC.

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