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Oral epithelial dysplasia and squamous cell carcinoma following allogeneic hematopoietic stem cell transplantation: clinical presentation and treatment outcomes

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Abstract

Background—Late complications of allogeneic hematopoietic stem cell transplantation (HSCT) include a risk of secondary malignancies, including oral cancers. Optimization of best clinical practices for early diagnosis and treatment of oral premalignant or malignant lesions requires an assessment of potential predisposing risk factors as well as treatment outcomes.

Methods—The medical records of patients who developed oral epithelial dysplasia (OED) and oral squamous cell carcinoma (OSCC) following allogeneic HSCT were reviewed. Data on demographics, HSCT course, chronic graft-versus-host disease (cGVHD), smoking and alcohol consumption, oral lesion characteristics, mode of therapy and clinical outcome were recorded; landmark survival was calculated.

Results—Twenty-six patients with OED (n = 8) and OSCC (n = 18) were identified with a median follow-up of 26.5 and 21.5 months, respectively. Premalignant and malignant oral lesions were diagnosed at a median time of 2.5 and 8 years after HSCT, respectively. Chronic GVHD was present in 96% of patients and of these, 96% had oral involvement. Multifocal oral cancer was

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found in 28% of cases, and localized recurrence was observed in 44% of cases. Five-year overall survival was 75% and 70% for OED and OSCC, respectively.

Conclusions—These results suggest that oral cGVHD may be considered a potential risk factor for the development of OSCC following allogeneic HSCT. The observation that oral cancers were frequently multifocal and recurred locally supports the concept of field cancerization and suggests that these cancers may be more aggressive compared with the non-HSCT population. Vigilant follow-up and coordination of care between hematologists and oral health specialists are critical to minimize morbidity and mortality.

Introduction

With improved outcomes after allogeneic hematopoietic stem cell transplantation (HSCT), increasing attention has been drawn to late complications in long-term survivors. Among these, survivors of allogeneic HSCT are at significantly increased risk for developing second cancers with the incidence of secondary solid tumors 2-6% at 10 years, and 6-13% at 15 years. (1-3)

Squamous cell carcinoma of the skin and mouth are the most common second solid malignancies, accounting for one-third of all secondary solid tumors, with oral squamous cell carcinoma (OSCC) representing 50% of these cases. (1, 2, 4) Curtis et al analyzed over 19,000 patients from the International Bone Marrow Transplant Registry and the Fred Hutchinson Cancer Research Center in the largest study of second cancers following allogeneic HSCT; the relative risk of OSCC was significantly increased in male patients (9.7), patients with chronic graft-versus-host disease (cGVHD; 6.0) and patients who received total body radiation as part of their conditioning regimen (3.0) as well as with time after HSCT (>10 years; relative risk 77.9). (1) Moreover, several case reports and small case series of OSCC following allogeneic HSCT have been reported. (2, 5-13) Possible mechanisms that have been proposed include radiation mutagenesis, cGVHD-related inflammation, prolonged immunosuppression from cGVHD therapy, immunological dysfunction, and carcinogenic and cytotoxic effects of immunosuppressive therapy, or a combination thereof. (8, 14, 15)

An improved understanding of the clinical features and potential factors associated with secondary OSCC, as well as its course and treatment outcomes, may be beneficial in better predicting, identifying and managing this very serious late toxicity of allogeneic HSCT. The objective of this study was to comprehensively review a multi-center cohort of patients who developed oral malignant lesions or oral epithelial dysplasia (OED) lesions after allogeneic HSCT.

Material and Methods

A retrospective review of clinical records was conducted for patients who had undergone allogeneic HSCT and were subsequently diagnosed with oral malignant or premalignant mucosal lesions. Non-epithelial cancers, such as post-transplantation lymphoproliferative disease, or relapsed hematologic malignancy with oral manifestations were excluded. Cases were collected from three transplantation centers: 1) Dana-Farber/Brigham and Women's

Cancer Center, Boston, USA; 2) Hadassah University Medical Center, Jerusalem, Israel; and 3) Bone Marrow Transplant Center, State University of Campinas, Campinas, Brazil. This study was approved by each center's institutional review board. All patients were transplanted between May 1980 and November 2007 and diagnosed with OED and OSCC lesions between May 1995 and March 2010.

Clinical data included HSCT course, cGVHD history, and details of OED and OSCC lesions, including presentation, staging (for carcinomas), management, and treatment outcomes. Tobacco and alcohol histories were obtained because these are well established risk factors in the non-HSCT general population. Oral lesions were classified into two categories: 1) OED, including verrucous hyperplasia (VH) and conventional dysplasia; and 2) malignant lesions (invasive carcinoma) including OSCC and verrucous carcinoma (VC, considered a histopathologic variant of squamous cell carcinoma).

Overall survival (OS) was calculated from the date of diagnosis of secondary oral changes or malignant oral disease to the date of death, censored at the date of last contact. Freedom from recurrence (FFR) was defined as the time from the date of diagnosis of malignant oral disease until the date of recurrence for patients with malignant oral disease, censored at the date of last contact. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Twenty-six patients with a median age of 49 (range 14-67) were diagnosed with oral OED or OSCC after allogeneic HSCT (Tables 1 and 2) with a median follow-up of 26.5 and 21.5 months, respectively. Three patients (12%) developed VH, 5 patients (19%) developed dysplasia and 18 patients (69%) developed invasive carcinoma. Twenty-four patients (96%) had cGVHD, and of these patients, 96% (23/24) presented with prominent oral features, requiring a variety of systemic and topical immunosuppressive and immunomodulatory therapies (Table 3). The median time from the first allogeneic transplantation to diagnosis of OED was 3 years for VH (range 1-13) and 2 years for dysplasia (range 1-3 years), whereas the median time to diagnosis of OSCC was 8 years (range 1-14 years; Table 4). Smoking and alcohol consumption was common in this cohort: 42% smoked or previously smoked and 35% regularly consumed alcohol (Table 5).

OED was most commonly observed on the lower lip, as a solitary lesion (Table 4). The median lesion dimensions at diagnosis were 2.0 × 1.0 cm and 1.0 × 1.0 cm for VH and dysplasia, respectively. All OED presented as leukoplakia (verrucous or otherwise), erythroleukoplakia, or proliferative verrucuous leukoplakia (Figure 1).(16) One case of dysplasia was associated with pain; all other cases of OED were asymptomatic. All premalignant lesions were treated surgically; one was treated with surgery followed by topical 5-fluorouracil (Figure 2).

Invasive carcinomas were predominately OSCC (n=15; 88%) with only 2 cases of VC observed (Figure 3 and 4; Table 5). Three cases of OSCC were preceded by a histopathological diagnosis of dysplasia (3/16, 19%; median time from dysplasia to OSCC

29 months, data not shown). The majority of invasive carcinomas (72%) were diagnosed as either Stage I or Stage II. The tongue was the most common site (n=10; 56%), followed by buccal mucosa (n=7; 39%) and lower lip (n=3; 17%); 28% presented with multifocal disease. Half of cases were purely white (50%), followed by red and white (44%) and purely red lesions (6%), and the median lesion size was 2.0 × 1.5 cm. The most frequent clinical features at diagnosis were plaques (50%), exophytic masses (39%) and ulcers (28%). Eleven cases (61%) presented with pain and two (11%) with paresthesia/anesthesia.

All but one case was managed with surgery with or without adjuvant radiation and/or chemoradiation therapy (Table 4). Eight cases (47%) had neck dissection as a part of the surgical management and only one patient had metastasis which involved the regional lymph nodes. Radiation therapy was not administered in 12 cases, including two Stage III cases (T3N0M0 and T3N0MX) and one Stage IVa (T4N0M0). This was in part due to concerns of further increasing the risk of cancer in the treatment field and in part due to favorable histopathologic features. In addition, in one T3 case radiation therapy was initiated but then discontinued due to cancer progression.

Outcomes are summarized in Table 6 and Figure 5. Local recurrence of invasive carcinoma occurred in 44% of cases with a median time to recurrence of 17 months (range 8-93) from the time of diagnosis. Five-year freedom from recurrence of invasive carcinoma was 46% (SE, 15%). In three cases (12%) a second primary OSCC occurred at a non-contiguous site from the original tumor. Five-year overall survival was 75% (SE, 22%) for patients with premalignant changes and 70% (SE, 14%) for patients with carcinoma. The median follow-up time for the entire cohort of patients was 47 months (95% CI 14-63).

Discussion

There are approximately 10,000 new cases of oral cancer in the US annually, with an incidence of 10.4 cases per 100,000 and overall five-year survival rate of 51.5%. (17, 18) The primary risk factors include tobacco and alcohol, with an emerging role for HPV infection in a subset of patients. (12, 15, 19, 20)

We were interested describing clinical characteristics and outcomes of OED and OSCC complicating long-term survivors of allogeneic HSCT. (8) The overall risk of second malignancies after allogeneic HSCT has been well reported in the literature in retrospective, observational and cohort studies. (1-3, 5, 21-34) However, details of the clinical aspects of oral cancers following HSCT have only been described in case reports or small case series. (4, 14, 35-37) This lack of information about the nature of oral cancer in this high-risk patient population has hindered clinical decision-making and the ability to develop preventive strategies and screening recommendations.

Most of our patients (24 out of 26 patients) developed cGVHD prior to the diagnosis of OED and OSCC, and in all but one of them (23 out of 24 patients) the oral tissues were involved. Eighty per cent of the patients with oral cGVHD received some type of localized therapy (e.g. topical steroids) specifically for their oral cGVHD, suggesting that the disease burden was considerable. The median interval from the diagnosis of oral cGVHD to the

diagnosis of oral cancer was six years. These findings support the model that the presence of cGVHD, and specifically in the oral mucosa, plays a significant role in the pathogenesis of oral cancer after allogeneic HSCT. Since GVHD is an alloimmune inflammatory process, long-term immunologically-mediated injury of the mucosa by T-cells may predispose to genomic instability and eventually to malignant transformation, particularly in the context of prior tobacco and alcohol use. (1) A recent study by Khan et al demonstrated genomic instability in oral, but not nasal (which is a rare site of cGVHD) cytological samples in patients with a history of cGVHD, providing both a direct role for cGVHD as well as a potential mechanism of oncogenesis, as genomic instability has been recently associated with epithelial malignancies. (1, 38-40) This may be more specifically mediated by long-term upregulation of cytokines, such as type I interferon, that are highly active in both cGVHD as well as OSCC. (41, 42, 39, 40) Furthermore, there is an emerging body of evidence suggesting that, at least in some cases of secondary solid cancers, donor-derived cells may play a role in carcinogenesis. (43, 44)

The majority of the patients with oral cGVHD were treated with topical and/or intralesional immunomodulators, including corticosteroids and calcineurin inhibitors (tacrolimus and cyclosporine). While there have been case reports of skin cancer developing following local treatment with topical tacrolimus, and two cases of oral cancer following intraoral topical therapy, a causal relationship remains uncertain. (45-50) Nonetheless, topical tacrolimus ointment has a FDA black box warning regarding its potential for increasing the risk of skin cancer. It has been suggested that topically applied tacrolimus may promote carcinogenesis through its immunosuppressive properties (51), by activating mitogen-activated protein kinase pathways (49), which promotes cell division, or by inhibiting keratinocyte DNA repair. (52) Systemic immunosuppressive therapy has also been identified as a potential risk factor for oral cancer; however similar to topical therapies, the exposure and the presence of cGVHD are closely interconnected and it therefore remains difficult to attribute any specific carcinogenic risk. There is no information about malignant transformation associated with the use of other topical immunosuppressive agents. Two patients from our series had previously been managed with localized intraoral ultraviolet B phototherapy for their oral cGVHD; however, unlike PUVA, this modality of therapy has not been associated with an increased incidence of skin cancer when used for the management of psoriasis and other inflammatory skin disorders.(53)

The majority of patients in our study were found to have low stage oral cancer (39% Stage I, 33% Stage II). It is noteworthy that most of these patients were routinely examined by oral medicine specialists, due to the presence of oral cGVHD. These frequent oral evaluations may have contributed to an earlier diagnosis of oral cancer, and perhaps to the favorable 5-year survival rate of 70%, compared with an overall five-year survival rate of 51.5% in the general population. (17, 18, 54)

Eight out of the 18 patients with oral cancer were complicated with a second oral cancer or recurrence of the first tumor. In the non-HSCT population, the incidence of second primary oral cancers is reported to be between 3% and 10%, compared with 45% in our series. (55, 56) Furthermore, in five patients the primary carcinoma was found in several foci. These findings suggest that the nature of oral cancer after allogeneic HSCT may be different and

possibly more aggressive than in non-HSCT patients, perhaps due to field changes (e.g. genomic instability) occurring as a result of long-standing oral mucosal inflammation, as well as underlying mutagenic injury from conditioning, alcohol, and tobacco use. (40, 43, 57) This is further supported by the fact that the buccal mucosa, one of the most commonly affected intraoral sites by cGVHD, was also one of the most frequent sites of OSCC in our series; however, buccal mucosa is not considered a high-risk site in non-HSCT patients. (58, 59) Despite these features, only one case had clinical evidence of lymph node metastasis on presentation. Although HPV testing was not performed in this study, none of the cases were located in the oropharynx, tonsils, or base of tongue, the three sites that have been linked epidemiologically to HPV 16 infection.(60)

There are several limitations of this study. First, due to the retrospective study design, data collection was limited to only those patients who had developed OSCC with the depth and accuracy of the available medical records. Second, although this study included a relatively large series of cancer cases, the number of patients with advanced stage (III and IV) tumors was insufficient to evaluate with respect to efficacy of treatment or the effect of treatment modality on the recurrence rate or survival. Considering that radiotherapy is a risk factor for cancer (42), the question remains as to whether radiotherapy should be employed for the treatment of oral cancer in patients with multiple other risk factors, such as conditioning regimen, underlying hematological malignant disease, cGVHD and treatment with immunomodulators. Lastly, while the goal of the study was to include all OED lesions in order to delineate the malignant potential of cGVHD, the actual risks of malignant transformation with dysplasia and VH are unknown. For this reason, cases of frank carcinoma were considered separately from dysplasia and VH.

In summary, this is a descriptive analysis of a large and highly characterized series of patients with OED and OSCC after allogeneic HSCT in which oral cGVHD may be considered a potential risk factor for oral cancer and demonstrates the aggressive nature of this serious late complication of allogeneic HSCT. Carefully coordinated long-term follow-up by a comprehensive cancer team that includes oral medicine expertise is recommended, and patients should be well-informed of cancer risk.(61) Large prospective multicenter studies are necessary to formally identify risk factors that can be used to develop preventive and screening strategies.

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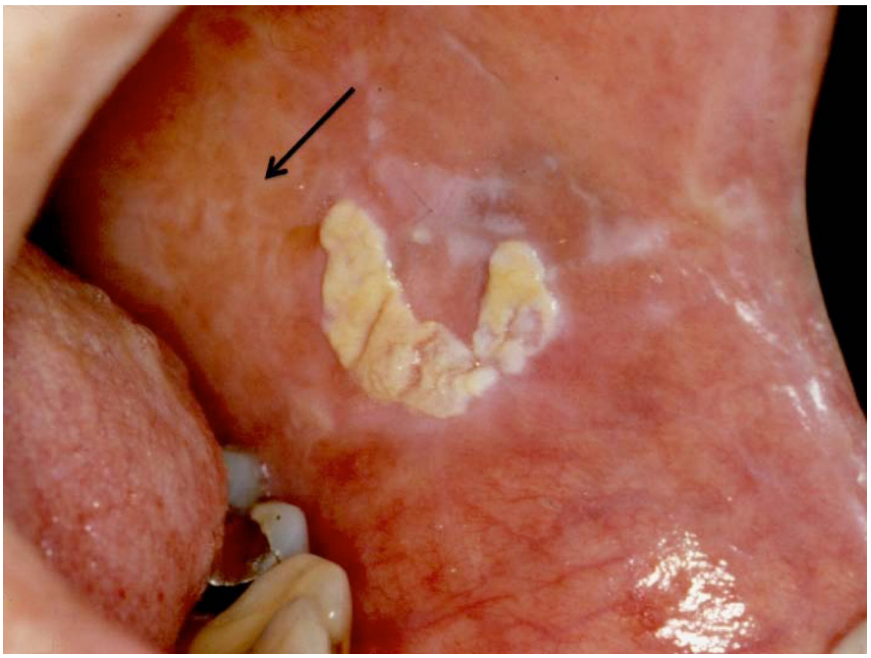

Figure 1.
Exophytic plaque on the left buccal mucosa that demonstrated verrucous hyperplasia histopathologically. Note the lighter white reticulations attributed to long-standing oral cGVHD (arrow).

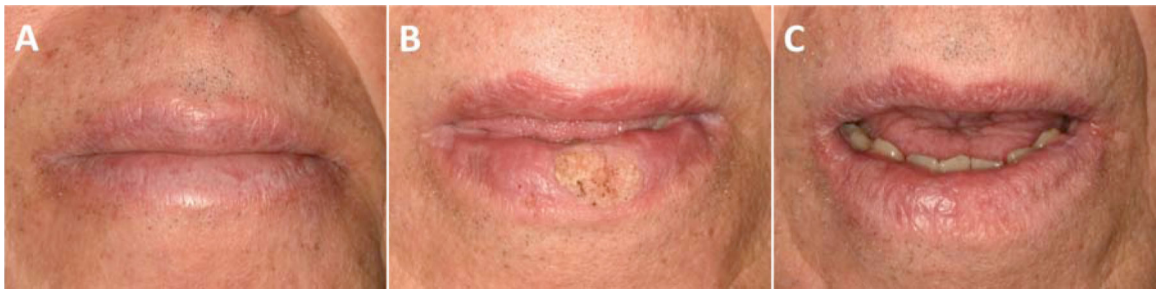

Figure 2.

Exophytic plaque on the lower lip that demonstrated dysplasia histopathologically (Day +390 post allo-HSCT) showing A) white reticular changes involving the uppper and lower lip; B) round dysplastic plaque on the lower lip; and C) complete healing of the lower lip dysplastic lesion after excision and topical treatment with 5-FU (Day +592).

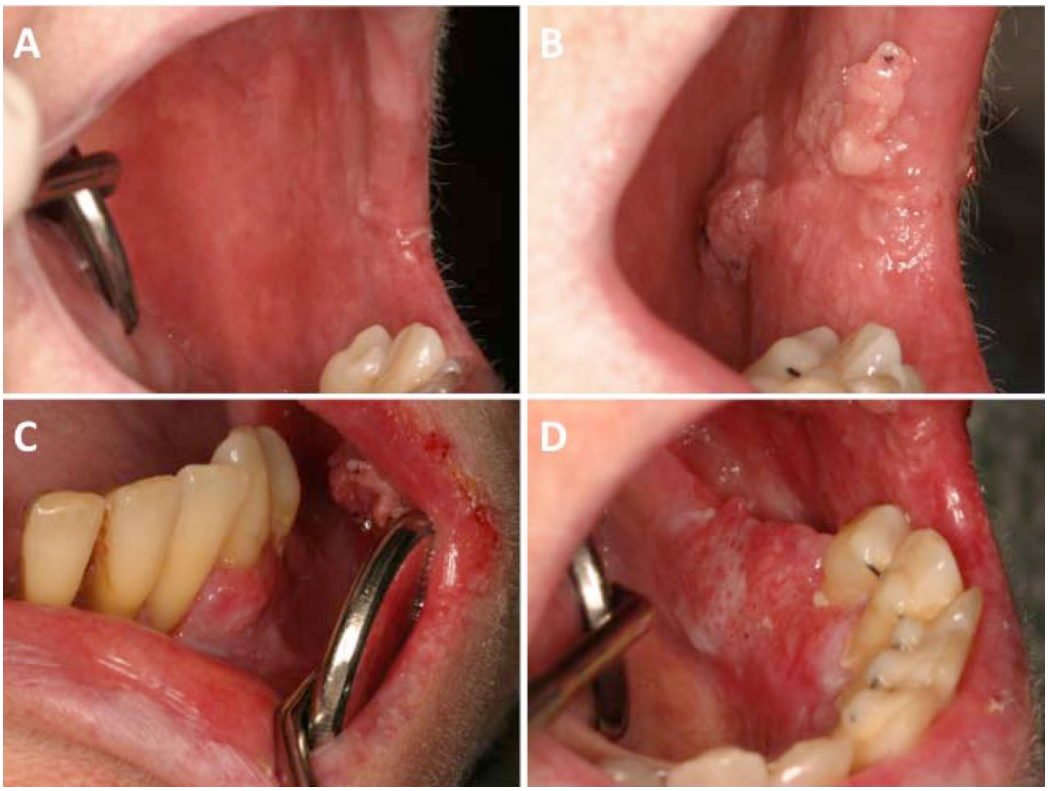

Figure 3.

Invasive squamous cell carcinoma that initially presented as persistent erythema of the left buccal mucosa (Panel A; Day +5080) that then developed into multiple pink exophytic verrucous masses (Panel B; Day +5290) as well as more flat, erythematous and speckled involvement of the right mandibular facial gingiva (Panel C) and left lingual alveolar ridge (Panel D).

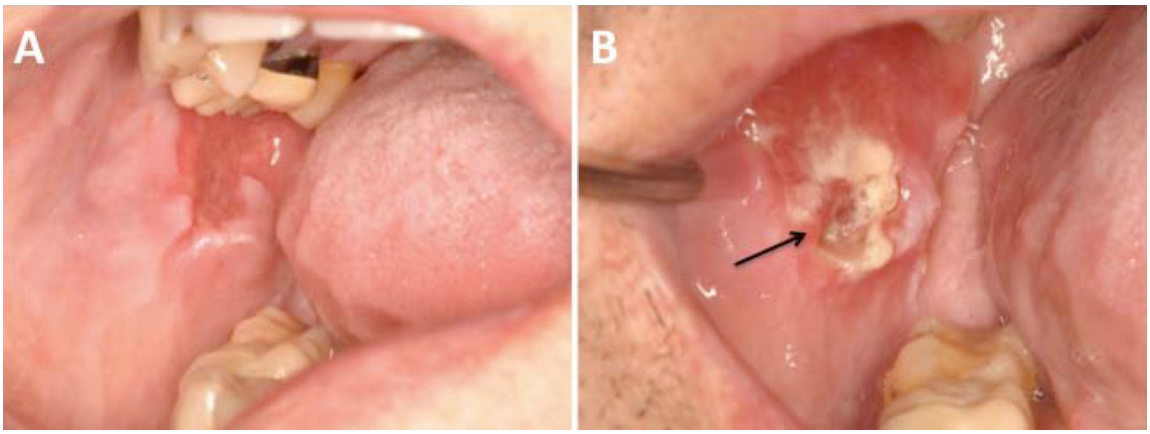

Figure 4.

Invasive squamous cell carcinoma of the right buccal mucosa. A) Lesion prior to biopsy that presented as a distinct area of erythema and atrophy in the context of bilateral oral cGVHD changes; B) painful, exophytic indurated white and red mass with focal ulceration (arrow).

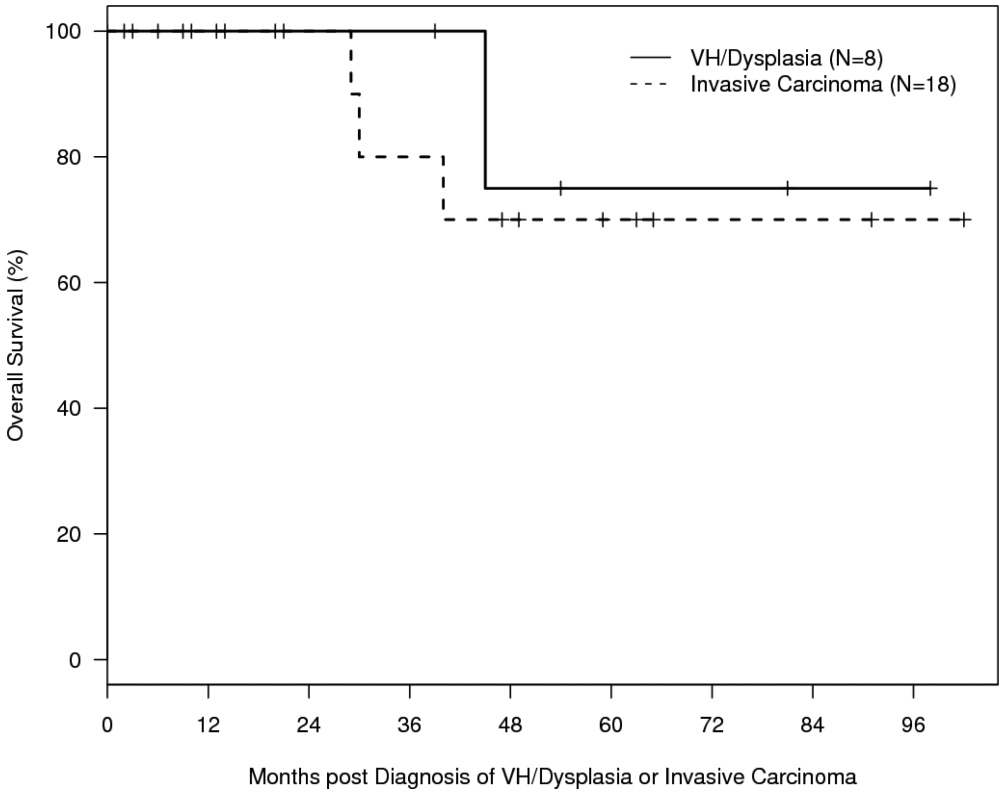

Figure 5A. Overall Survival

Kaplan-Meier curve of overall survival (OS) for patients who developed VH/dysplasia (N = 8) or invasive carcinoma (N = 18) post-HSCT. Curves are calculated from the time of diagnosis of VH/dysplasia or invasive carcinoma.

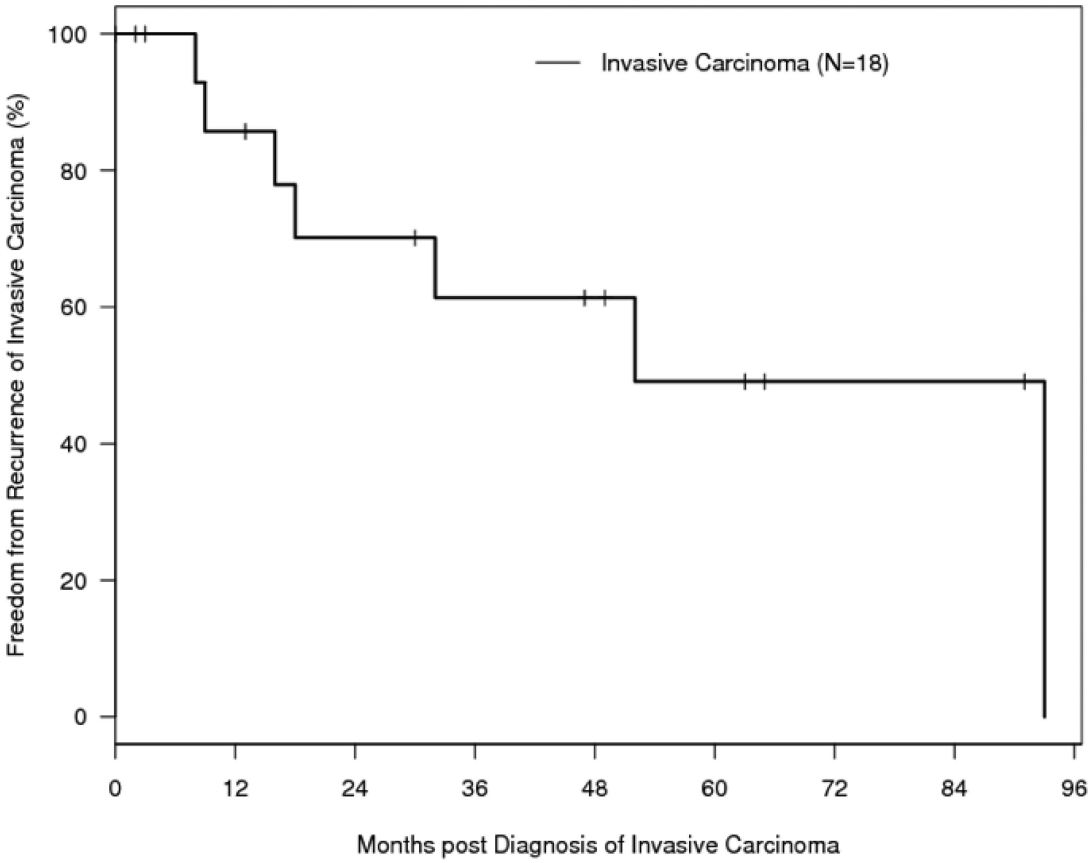

Figure 5B. Freedom from Recurrence (FFR)

Kaplan-Meier curve of freedom from recurrence (FFR) for patients who developed invasive carcinoma (N = 18) post-HSCT. Curves are calculated from the time of diagnosis of invasive carcinoma.

Table 1

Patient Distribution

Institute	No. of Patients (N=26)	Verrucous hyperplasia	Dysplasia	Invasive carcinoma
Dana-Farber/Brigham and Women's Cancer Center, Boston, USA	16 (62%)	3 (19%)	3 (19%)	10 (63%)
Hadassah University Medical Center, Jerusalem, Israel	7 (27%)	-	2 (29%)	5 (71%)
Bone Marrow Transplant Center, State University of Campinas, Campinas, Brazil	3 (12%)	-	-	3 (100%)

Table 2

Patient Characteristics

	N (%)
N	26
Age, median (range)	49 (14, 67)
Sex	
Female	7 (27)
Male	19 (73)
Primary diagnosis	
CML	9 (35)
NHL	5 (19)
AML	4 (15)
AA	2 (8)
CLL	2 (8)
ALL	1 (4)
MDS	1 (4)
MM	1 (4)
NHL/MDS†	1 (4)
Cases with >1 HSCT (Type of 1st Transplant)	7 (27)
Autologous	6 (23)
Allogeneic	1 (4)
Type of conditioning for 1st allogeneic HSCT††	
Myeloablative	14 (54)
Cy/TBI	13 (50)
Flu/TBI	1 (4)
Non-myeloablative	12 (46)
Bu/Cy	4 (15)
Cy	1 (4)
Bu/Flu	6 (23)
Bu	1 (4)
No conditioning†††	1 (4)

Abbreviations: CML=chronic myeloid leukemia; NHL=non-Hodgkin lymphoma; AML=acute myeloid leukemia; AA=aplastic anemia; CLL=chronic lymphocytic leukemia; ALL=acute lymphocytic leukemia; MDS=myelodysplastic syndrome; MM=multiple myeloma; Bu= busulfan, Cy= cyclophosphamide, Flu= fludarabine; N/A= not available.

† Patient was originally diagnosed with NHL, treated with autologous HSCT, and was subsequently diagnosed with secondary MDS and underwent non-myeloablative allogeneic HSCT.

†† For patients who underwent multiple allogeneic transplants, only their first conditioning regimen is provided.

††† After the first myeloablative autologous HSCT, the patient was subsequently treated with a DLI which resulted in marrow aplasia. No further conditioning was given prior to the second allogeneic HSCT.

Table 3

Summary of cGVHD Summary

	N (%)
Number of patients with history of cGVHD	24 (96)
Sites of cGVHD†	
Skin	23 (96)
Oral	23 (96)
Eyes	11 (46)
GI	10 (42)
Hepatic	9 (38)
Pulmonary	3 (13)
Myofascial	1 (4)
Vaginal	1 (4)
Systemic cGVHD treatment†	
Corticosteroids	23 (96)
Calcineurin inhibitors	23 (96)
Mycophenolate mofetil	7 (29)
Azathioprine	6 (25)
Phototherapy (ECP/PUVA)	5 (21)
Thalidomide	2 (8)
Rapamycin	1 (4)
Oral cGVHD	23 (96)
Time to onset since allogeneic HSCT in months, median (range)††	7 (1, 23)
Time from oral cGVHD to diagnosis of dysplasia in years, median (range)	0.8 (0.6, 2.1)
Time from oral cGVHD to diagnosis of VH in years, median (range)	0.95 (0.1, 1.8)
Time from oral cGVHD to diagnosis of malignancy in years, median (range)	6 (1, 14)
Topical oral cGVHD ancillary treatment†	
Corticosteroids	16 (69)
Calcineurin Inhibitors	6 (26)
UVB	2 (9)

Abbreviations: ECP = extracorporeal photopheresis; PUVA = psoralen-ultraviolet A phototherapy; VH = verrucous hyperplasia; UVB = ultraviolet B phototherapy.

† Multiple sites or treatments per patient are possible, so the frequencies do not sum to N=23 and the percentages do not sum to 100%.

†† Time to oral cGVHD was calculated from the date of the corresponding allogeneic HSCT; only 18 patients had the date of onset available.

Table 4

Characteristics and Management of Oral Lesions.

	Verrucous hyperplasia	Dysplasia	Invasive carcinoma
N	3	5	18
Time to Development in years, median (range)†	3 (1, 13)	2 (1, 3)	8 (1, 14)
Cancer Stage			
Stage I (T1N0M0)	-	-	7 (39)
Stage II	-	-	6 (33)
T2N0M0			5 (28)
T2N1M0	-	-	1 (6)
Stage III	-	-	4 (22)
T3N0M0	-	-	2 (11)
T3N0MX	-	-	2 (11)
Stage IVa (T4N0M0)	-	-	1 (6)
Focal versus Multifocal			
Focal	2 (67)	5 (100)	13 (72)
Multifocal	1 (33)	0 (0)	5 (28)
Location††			
Tongue	0 (0)	1 (20)	10 (55)
Lower Lip†††	0 (0)	4 (80)	3 (17)
Buccal mucosa	1 (33)	0 (0)	7 (39)
Gingiva	2 (66)	0 (0)	4 (22)
Hard Palate	1 (33)	0 (0)	1 (5)
Alveolar mucosa	0 (0)	0 (0)	2 (10)
Color			
Red	0 (0)	0 (0)	1 (6)
Red/White	0 (0)	2 (40)	8 (44)
White	3 (100)	3 (60)	9 (50)
Clinical appearance††††			
Plaque	3 (100)	2 (40)	9 (50)
Exophytic	0 (0)	0 (0)	7 (39)
Ulceration	0 (0)	2 (40)	5 (28)
Papillary	0 (0)	2 (40)	2 (11)
Crusting	0 (0)	2 (40)	1 (6)
Erythema	0 (0)	0 (0)	3 (17)
Pain	0 (0)	1 (20)	11 (61)
Anesthesia/Paresthesia	0 (0)	0 (0)	2 (11)
Management			
Surgery alone	3 (100)	4 (80)	12 (67)
Surgery/Radiotherapy	0 (0)	0 (0)	1 (6)
Surgery/topical 5FU	0 (0)	1 (20)	0 (0)

	Verrucous hyperplasia	Dysplasia	Invasive carcinoma
Surgery/Chemotherapy/Radiotherapy	0 (0)	0 (0)	4 (22)
Chemotherapy/Radiotherapy	0 (0)	0 (0)	1 (6)

† Measured from the date of the 1st allogeneic transplant to the date of development of initial SCC. The overall median was 5 years (range 1-14).

†† There may have been multiple sites involved per patient, so the frequencies do not sum to N=26 and the percentages do not sum to 100%.

††† All lesions appeared to originate on the lip; 3 out of 7 cases also extended to the labial mucosa intraorally.

†††† There may have been multiple clinical features per patient, so the frequencies do not sum to N=25 and the percentages do not sum to 100%.

Table 5

Tobacco and Alcohol History

	N (%)
Smoking status	
Daily smoker	4 (15)
Former smoker	7 (27)
Non-smoker	15 (58)
Alcohol consumption	
Occasion (1-2 drinks/wk)	8 (31)
Daily (6-7 drinks/wk)	1 (4)
None	17 (65)

Table 6

Outcome Summary

	VH/Dysplasia	Invasive Carcinoma
No. of Patients	8	18
Recurrence of Invasive Carcinoma	N/A	8 (44)
New site	N/A	5 (28)
Same site	N/A	3 (12)
5 year FFR ± SE (%)†	N/A	46 ± 15
5 year OS ± SE (%)††	75 ± 22	70 ± 14
Time to Recurrence in months, median (range)	N/A	17 (8, 93)

†SE: Standard error; FFR = Freedom from recurrence. FFR was calculated from the date of diagnosis of invasive carcinoma to the date of recurrence.

††OS = Overall survival; OS was calculated from the date of diagnosis of secondary oral changes to the date of death.