Oral Oncology 60 (2016) 125–129

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Should severe epithelial dysplasia be treated?

Lewei Zhang [a,b,c,*], Tarinee Lubpairee [a,c], Denise M. Laronde [a,c], Miriam P. Rosin PhD [c,d,*]

[a] Faculty of Dentistry, The University of British Columbia (BC), 2199 Wesbrook Mall, Vancouver, BC V6T 1Z3, Canada
[b] BC Oral Biopsy Service, Department of Laboratory Medicine and Pathology, Vancouver General Hospital, 910 West 10th Avenue, Vancouver, BC V5Z 1M9, Canada
[c] BC Oral Cancer Prevention Program, BC Cancer Agency, Vancouver, BC V5Z 1L3, Canada
[d] School of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, BC V5A 1S6, Canada

ARTICLE INFO

Article history:
Received 26 May 2016
Accepted 12 July 2016
Available online 22 July 2016

Keywords:
Oral cancer
Oral premalignant lesions
Dysplasia
Treatment
Cancer progression

ABSTRACT

Objective: To identify clinical features associated with progression of primary severe epithelial dysplasia into invasive squamous cell carcinoma (SCC).
Design: Longitudinal population-based study.
Setting: Oral dysplasia clinics.
Patients: This study involved 118 patients with 118 severe dysplasia who were prospectively enrolled between 1996 and 2014, and the lesions were either completely removed surgically (treated) or actively followed (untreated).
Measurements: Demographics, habits, clinical information and outcome were compared between the treated and untreated groups.
Results: Of the 118 lesions, 77 were treated and 41 were not. The treated lesions showed significantly less progression when compared to the untreated: 5/77 (6%) treated lesions progressed into invasive SCC versus 12/41 (29%) untreated ($P = 0.004$). The 5-year probability (confidence interval) of progression into SCC for the treated was 7.6 (1–14) as compared to 38.6 (16–55) for the untreated. Interestingly the clinical changes at the site of the disease also had strong predictive value for cancer progression. If the site showed no lesion after treatment or after incisional biopsy (40 cases), only 1 (3%) progressed into cancer. If the site showed ever disappearance of the lesion or marked decrease in the size of the lesion to $\leqslant$10 mm (29 cases), 4 (15%) progressed. If the site showed lesions with fluctuation in size or persistent in size or marked increase in size (25 cases), 18 (58%) progressed ($P < 0.001$).
Conclusion: Treatment significantly reduced cancer progression, and phenotypic changes at the site of the disease had significant predictive value for cancer progression.

Introduction

Severe oral epithelial dysplasia is a late stage premalignant/preinvasive lesion that is believed to have a high cancer progression rate. Despite consensus on the seriousness of the disease, few studies have focused specifically on this stage of disease and its management. The literature in this area is very controversial. In addition, some studies have not broken down analysis by histological diagnosis, not allowing for easy identification of impact on severe dysplasia. The total number of severe dysplasia reported on in all studies together is very small.

Table 1 showed studies that had included severe dysplasia and compared the outcome of surgically treated and not treated dysplasia. Most such studies showed no significant difference between treated and untreated groups [1–5], although some studies showed a higher cancer rate in the treated group: Arduino et al. [2] reported a cancer progression rate in the surgically treated group (9.0%) that was more than twice that of the untreated group (4.1%, $P = 0.265$); Holmstrup et al. [3] showed similar results with cancer progression in the surgically treated group (10.2%) almost three times higher than that in the untreated group (3.6%) ($P = 0.084$, approaching significant). In contrast, two studies did show significant reduction of cancer progression by surgical treatment. Banoczy and Csiba [4] reported that only 1 of 46 (2.2%) surgically treated dysplastic lesions progressed into cancer as

Abbreviations: SCC, squamous cell carcinoma; CIS, carcinoma *in situ*; BC, British Columbia.

* Corresponding authors at: Faculty of Dentistry, The University of British Columbia (BC), 2199 Wesbrook Mall, Vancouver, BC V6T 1Z3, Canada.
E-mail addresses: lzhang@dentistry.ubc.ca (L. Zhang), tarineel@gmail.com (T. Lubpairee), dlaronde@dentistry.ubc.ca (D.M. Laronde), mrosin@bccrc.ca (M.P. Rosin).

http://dx.doi.org/10.1016/j.oraloncology.2016.07.007
1368-8375/

Table 1
Studies compared outcomes of treated and not treated dysplasia.

Source	Follow up time (mon)	Dx[a]	All #	Treated[b] (removed)		Not treated (not removed)		Chi-square *P* value[c]
				Total	To cancer	Total	To cancer	
Arduino et al. [2]	At least 12, medium 54	D3[d]	22	16	1 (6.7%)	6	0 (0%)	*0.104*
		D2[e]	50	37	5 (13.5%)	13	2 (15.4%)	
		D1[f]	135	80	6 (7.5%)	55	1 (1.8%)	
		All	207	133	12 (9.0%)	74	3 (4.1%)	*0.265*
Arnaoutakis et al. [1]	Mean 59	D1 to CIS[g]	112[h]	70	16 (23%)	42	16 (38%)	***0.04 (HR: 0.43)***
		D1 to CIS	58[i]	16	3 (19%)	42	16 (38%)	***0.02 (HR: 0.14)***
Banoczy & Csiba [4]	Mean 76	D3	12	6	1 (16.7%)	6	4 (66.7%)	
		D2	43	29	0 (0%)	14	3 (21.4%)	
		D1	13	10	0 (0%)	3	1 (33.3%)	
		All	68	46	1 (2.2%)	22	8 (36.4%)	***<0.003***
Holmstrup et al. [3]	Mean 79	D3	14	11	1 (9.1%)	3	0 (0%)	
		D2	26	22	2 (9.1%)	4	0 (0%)	
		D1	42	28	3 (10.7%)	14	2 (14.3%)	
		H	116	27	3 (11.1%)	89	2 (2.2%)	
		All	198	88	9 (10.2%)	110	4 (3.6%)	*0.084*
Mincer et al. [5]	12–90	D2, D3, CIS	45	23	3 (13.0%)	22	2 (9.1%)	*1.000*

The bold *P* values indicate that the *P* value is ≤ 0.05, which is statistically significant as defined in Statistical Analysis in Materials and Methods.
[a] Dx = diagnosis.
[b] Treatment is defined as removal of the lesion by blade, laser or cryosurgery.
[c] *P* values were determined from Chi-square except for the study from Arnaoutakis et al. [1], which was determined by hazard ratio.
[d] D3: severe dysplasia.
[e] D2: moderate dysplasia.
[f] D1: mild dysplasia.
[g] CIS: carcinoma *in situ*.
[h] Wide excision.
[i] Laser excision.

compared to 8 of 22 (36.4%) untreated dysplastic lesions. A more recent study by Califano's group [1] showed that in comparison to observation, both wide local excision (HR 0.43, $P = 0.04$) and laser treatment (HR 0.14, $P = 0.02$) of dysplastic lesions significantly reduced progression to cancer. With such conflicting results, it is not surprising that The World Workshop on Oral Medicine IV concluded, based on a literature review covering 40 years of studies by Brennan et al. [6], that 'Because of the lack of randomized controlled trials that have shown effectiveness in the prevention of malignant transformation, no recommendations can be provided for specific surgical interventions of dysplastic oral lesions'.

This study reports on findings within the ongoing Oral Cancer Prediction Longitudinal study in British Columbia, Canada that has been following cases of dysplasia to outcome since 1996. The overall goal of that study was to identify clinical (with emphasis on treatment) features that are associated with progression of primary severe epithelial dysplasia to oral cancer. Treatment options within this study were left to the study clinicians, with patients monitored for outcome. Here we report on the effect on outcome of complete removal of severe dysplasia in comparison to its active surveillance.

Materials and methods

Patient population

This population-based study involved patients who were prospectively enrolled in the ongoing longitudinal study in Vancouver, British Columbia (BC), Canada between 1996 and 2013. Accrual to this cohort was from community practices across BC (population, 4·1 million in 2011). Patients were identified primarily through a centralised pathology service, the BC Oral Biopsy Service, which receives biopsies from dentists and ENT surgeons across the province. This population-based biopsy service receives 250–300 dysplasia cases annually. Patients with dysplastic lesions were referred to five Oral Dysplasia Clinics in Greater Vancouver where they were accrued to the study using written informed consent and a study protocol approved by the UBC/BCCA (University of BC/BC Cancer Agency. Institutional Research Board. The analysis in this paper focused on patients with a histological diagnosis of severe dysplasia in the oral cavity with no prior history of oral cancer. A total of 118 patients with 118 lesions met these study criteria and were followed for up to 100 months. The mean follow-up time was 52 ± 33 months with outcome either SCC or carcinoma *in situ* (CIS) or 57 ± 32 months when outcome was only SCC. During the study period, 29 (25%) of these cases progressed, 13 to *CIS*, and 16 to invasive SCC. Of the 13 cases that progressed to *CIS*, one later went on to develop SCC.

Clinical pathological data, treatment and follow-up

The longitudinal study collects demographic data, clinical information, as well as tobacco and alcohol habits at study entry. Patients were followed at six month intervals. At each follow up, oral lesions were examined and any worrisome changes were re-biopsied. Treatment was defined as complete removal of severe dysplasia, including both complete clinical removal and histological margins free of severe dysplasia. The primary endpoint of this study was time from index biopsy to histologically confirmed progression to either *CIS* or SCC, or invasive SCC only at the same anatomical site as the index biopsy.

Statistical analysis

Associations between the two study groups and progression, as well as the demographic and clinical differences between the two groups were examined using Fisher's exact test, or an unpaired *t* test (age and follow-up time). Time-to-progression curves were estimated by the Kaplan-Meier method, and comparisons were performed using log-rank test. Hazard ratios (HRs) and the corresponding 95% confidence intervals (95% CI) were determined using Cox regression analysis. $P \leqslant 0.05$ was considered significant.