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Should severe epithelial dysplasia be treated?

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Summary

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

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CONFLICT OF INTEREST

None declared.

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disappearance of the lesion or marked decrease in the size of the lesion to 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.

Keywords

oral cancer; oral premalignant lesions; dysplasia; treatment; 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 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 to 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. $P < 0.05$ was considered significant.

Results

Of the 118 patients, 77 (65%) had their severe dysplasia completely removed by surgical blade or laser (hereafter termed the "treated group") while 41 (35%) received only active surveillance (the "untreated group"). Table 2 compares patient characteristics in the two

groups, including demographics, habits, site and size of the lesions, outcome and follow up times.

There were no significant differences in age, gender, ethnicity and habit of the patients in treated and the untreated groups, nor were there any significant differences in the site and size of the lesions between the two groups.

The treated group showed significantly less progression to cancer when compared to the untreated group. When the end point was either CIS or SCC, the untreated lesions showed a 6.1-fold increase in relative cancer risk when compared to the treated lesions ($P < 0.001$, Fig. 1). When the end point was only invasive SCC (end point of CIS was designated as no progression), the untreated lesions showed a 4.9-fold increase in relative cancer risk when compared to the treated lesions ($P = 0.002$, Fig. 1).

There were significant differences in follow up time: the treated lesions were followed up significantly longer: mean follow up time 62 ± 30 versus 34 ± 29 months in the untreated lesions when the outcome was defined as SCC/CIS ($P < 0.001$); or 65 ± 30 versus 43 ± 32 months in untreated lesions when the outcome was restricted to SCC ($P = 0.002$). Similarly a longer time (around one year) was noted for the treated lesions to progress to cancer as compared to the untreated lesions: 35 vs 23 months when outcome was CIS/SCC or 37 vs 25 months when outcome was only invasive SCC, although the difference was not significant ($P > 0.05$).

Table 3 compares the probability of progression in treated and untreated lesions, showing 1-, 3- and 5-year rates and CIs. Strikingly, while no cases progressed to CIS or SCC in the first year of follow-up in the treated group, progression rates in the untreated group were 22.9% (when the outcome was defined as SCC/CIS) and 10.0% (when the outcome was restricted to invasive SCC). This difference was also apparent for both 3- and 5-year probabilities with lower rates for treated compared with untreated lesions, when the outcome was defined as CIS/SCC (3-year of progression: 5.6% vs 31.7%; 5-year: 14.0% vs 59.8%) and also when the outcome was defined as only invasive SCC (3-year: 5.7% vs 23.4%; 5-year 7.6% vs 38.6%).

We also looked at influence of how timely the first treatment was with respect to progression. The median time from the index biopsy to first treatment was 3 months, ranging from 0, i.e., treatment at the first biopsy (index biopsy), to 74 months. The median time from the index biopsy to first treatment was not significantly different between the two groups (4 months in progressed group vs 3 months in non-progressed group; $P = 0.93$).

According to the morphological changes at the index site (site of severe dysplasia), we have grouped the patients into 3 group. Group 1 (40 patients) included cases in which the lesion disappeared. Thirty-six of these cases had been treated and were clinically and histological clear after treatment, with no clinical recurrence during follow-up. An additional 4 cases belonged to the untreated group but had a complete regression of the lesion. All 4 of these latter cases were < 2 cm in diameter: One case had no clinical lesion remaining after removal of the diagnostic biopsy, however, histologically the lesion involved the biopsy margins; two cases showed no lesion at the first recall examination and thereafter even

though the biopsy was incisional; the fourth case showed a lesion at the 3rd and 8th month but not at the 14th month and later recalls.

Cases were placed into Group 2 (27 patients) when there appeared to be a tendency towards remission in the lesions: the lesions either disappeared completely sometime or showed an obvious persistent decrease in size to 10 mm in the largest diameter.

Group 3 (31 patients) included lesions which fluctuated in size but never disappeared, or were unchanged in size, or increased in size.

Outcome for the lesion was highly dependent on changes at the index sites overtime. The group 1 lesions had the best prognosis: only 1 case (3%) progressed: this case was treated and after the treatment the patient had no lesion for almost 3 years, and the first time a lesion appeared, it was a CIS. Group 2 had a 15% progression rate, treatment reduced the rate of progression rate to 6% compared to untreated cases that had a 33% progression rate. Group 3 had the worst prognosis, with a 58% progression rate. Even after treatment, the progression rate was still 46% with 75% progression rate in the untreated group (all $P < 0.0001$).

Time-to-progression curves for the 3 groups of lesions were estimated by the Kaplan-Meier method (Fig. 2). When compared to Group 1 lesions, Group 2 lesions showed 6.3-fold increase in relative cancer risk and Group 3 35.9-fold increase in relative cancer risk ($P = 0.1$ and $P = 0.0004$ respectively).

Discussion

Severe dysplasia is considered to be a histologically defined lesion that has the greatest risk of progression among lesions diagnosed to have oral potentially malignant disease. Yet few studies have investigated the natural history of this disease state, or provided clear evidence supporting its treatment. Table 4 lists data from these limited studies in which the outcome of surgically treated severe dysplasia was compared with untreated severe dysplasia. Although some studies showed that treatment did not make a difference in outcome, overall untreated lesions were more than twice as likely to progress into cancer.

Our research is a population based longitudinal study that represents the largest investigation of severe dysplasia to date. The data presented in this analysis demonstrates that surgical removal of the severe dysplasia significantly reduced cancer progression of the disease: the untreated lesions had either a 6.1-fold increase in cancer risk when outcome included both invasive cancer (SCC) and non-invasive cancer (CIS), or a 4.9-fold increase in cancer risk when outcome was restricted to SCC only. The 5-year probability of progression to invasive SCC of the untreated group (38.6%) was more than 5 times greater than that of the treated group (7.6%); the 3-year probability for the untreated group (23.4%) was more than 4 times of that of the treated group (5.7%), and at one year, the probability of progression for the untreated lesions was 10% whereas none of the treated lesions progressed. Furthermore, even for those treated lesions that later progressed, treatment delayed the cancer progression by about one year.

It is interesting to note that despite the high progression rate in untreated lesions (46%), a little more than half (54%) of the lesions did not progress during follow-up. This result was similar to that reported in a recent study by Califano's group, [1], where 50% of untreated lesions also did not progress. Our study showed that phenotypic changes as observed at the index sites may help to identify those that might have lower cancer risk despite of no treatment, or to assess the chance of progression in treated cases. For example, when the index sites showed no lesion after treatment or after an incisional biopsy, the progression rate was very low (3%). The next best scenario was when the index site showed a tendency of remission (either completely disappear sometimes or decrease in size to 10 mm in diameter), the overall progression rate was 15% with treatment resulting in excellent prognosis (progression rate 6%); whereas the untreated had 33% of progression rate. The worst scenario was when the index sites showed persistence of the lesions (fluctuated in size, or remained the same in size or increased in size), the overall progression rate was 58%. Even treated sites in this group had a high progression rate of 46%; whereas those untreated showed a very high progression rate of 75%.

In conclusion, this study sheds much needed light on the natural history of severe dysplasia and also on the treatment effect on the progression. If the results are confirmed by future multi-centre trial, it would indicate that severe dysplasia should be treated if possible.

Acknowledgments

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Abbreviations

SCC	squamous cell carcinoma
CIS	carcinoma <i>in situ</i>
BC	British Columbia

Highlight

- Complete surgical removal of severe epithelial dysplasia reduced its cancer progression rate.
- Morphological changes at the index site predicted outcome of the lesion

Figure 1.
Kaplan-Meier by treatment.

Figure 2.

Kaplan-Meier by lesion morphological changes overtime. For Group 1, the index sites showed no lesion after treatment or after an incisional biopsy. For Group 2, the index site showed a tendency of lesion remission (either completely disappear sometimes or decrease in size to 10 mm in diameter). For Group 3, the index sites showed persistence of the lesions (fluctuated in size, or remained the same in size or increased in size).

Table 1

Studies compared outcomes of treated and not treated dysplasia

Source	Follow up time (mon)	Dx ¹	All #	Treated ² (removed) total	to cancer	Not treated (not removed) total	to cancer	Chi-square P value ³
Arduino <i>et al.</i> , 2009	at least 12, medium 54	D3 ⁴	22	16	1 (6.7%)	6	0 (0%)	0.104
		D2 ⁵	50	37	5 (13.5%)	13	2 (15.4%)	
		D1 ⁶	135	80	6 (7.5%)	55	1 (1.8%)	
		all	207	133	12 (9.0%)	74	3 (4.1%)	
Amaoutakis <i>et al.</i> , 2013	Mean 59	D1 to CIS ⁷	112 ⁸	70	16 (23%)	42	16 (38%)	0.04 (HR: 0.43)
		D1 to CIS	58 ⁹	16	3 (19%)	42	16 (38%)	0.02 (HR: 0.14)
Banoczy & Csiba, 1976	Mean 76	D3	12	6	1 (16.7%)	6	4 (66.7%)	< 0.003
		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%)	
Holmstrup <i>et al.</i> , 2006	mean 79	D3	14	11	1 (9.1%)	3	0 (0%)	0.084
		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%)	
Mincer <i>et al.</i> , 1972	12 - 90	all	198	88	9 (10.2%)	110	4 (3.6%)	1.000
		D2, D3, CIS	45	23	3 (13.0%)	22	2 (9.1%)	

¹ Dx = diagnosis.² Treatment is defined as removal of the lesion by blade, laser or cryosurgery.³ P values were determined from Chi-square except for the study from Amaoutakis *et al.*, 2013, which was determined by hazard ratio.⁴ D3: severe dysplasia.⁵ D2: moderate dysplasia.⁶ D1: mild dysplasia.

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7 CIS: carcinoma *in situ*.
8 Wide excision.
9 Laser excision.

Table 2

Demographics, habits and outcome in treated and untreated groups

Characteristics	All N = 118	Treated N = 77	%	Untreated N = 41	%	P value
Age (median)	57 (34 - 88)	55 (34 - 83)		59 (38 - 88)		0.15
Gender						
Male	60	38	49%	22	54%	0.7
Female	58	39	51%	19	46%	
Ethnicity						
White	97	64	83%	33	80%	0.8
Non-white	21	13	17%	8	20%	
Habit						
Never smokers	37	28	36%	12	29%	0.54
Ever smokers	78	49	64%	29	71%	
Site						
Ventrolateral tongue/FOM ¹	99	67	87%	32	78%	0.29
Other sites	19	10	13%	9	22%	
Size (diameter in mm)						
Mean $\pm$ SD	303 $\pm$ 403	282 $\pm$ 370		345 $\pm$ 465		0.48
Median (range)	144 (5-2262)	144 (5-2160)		162 (24-2262)		
Outcome defined as SCC ² /CIS ³						
Outcome						
Prog ⁴	29	10	13%	19	46%	< 0.001
Not prog	89	67	87%	22	54%	
Follow up time						
All cases: mean $\pm$ SD	52 $\pm$ 33	62 $\pm$ 30		34 $\pm$ 29		< 0.001
Prog: mean $\pm$ SD	28 $\pm$ 22	35 $\pm$ 21		23 $\pm$ 21		
Outcome defined as SCC						
						0.14

4 Prog: progression.

Table 3

Probability of progression for treated and untreated lesions

Probability of progression to cancer	All N = 118	Treated N = 77	Untreated N = 41
Outcome defined as SCC¹/CIS²			
<i>1-year (95% CI)</i>	7.8 (2.8- 12.6)	0	22.9 (8.5-35.0)
<i>3-year (95% CI)</i>	14.4 (7.6-20.8)	5.6 (0.1-10.9)	31.7 (15.0-45.1)
<i>5-year (95% CI)</i>	27.6 (17.8-36.2)	14.0 (5.0-22.2)	59.8 (33.1-75.9)
Outcome defined as SCC			
<i>1-year (95% CI)</i>	3.4 (0 - 7)	0	10.0 (0 - 19)
<i>3-year (95% CI)</i>	11.4 (5 - 17)	5.7 (0 - 11)	23.4 (7 - 37)
<i>5-year (95% CI)</i>	16.8 (9 - 24)	7.6 (1 - 14)	38.6 (16 - 55)

¹SCC; squamous cell carcinoma.²CIS: carcinoma *in situ*.

Table 4

Studies comparing outcome of the treated and untreated severe dysplasia

Source	Follow up time (mon)	All #	Treated (% progression)		Not treated (% progression)		P value
			Total	Progress	Total	Progress	
Arduino et. al. 2009	At least 12, median 54	22	16	1 (6.7%)	6	0 (0%)	1.00
Amaoutakis et. al. 2013	Mean 59	29	21	5 (24.0%)	8	4 (50.0%)	0.21
Banoczy and Csiba, 1976	Mean 76	12	6	1 (16.7%)	6	4 (66.7%)	0.24
Holmstrup et. al. 2006	Mean 79	14	11	1 (9.1%)	3	0 (0%)	1.00
All		77	54	8 (14.8%)	23	8 (34.8%)	0.07