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CITATION: Ellonen, R., Kelppe, J., Hagström, J., Suominen, A., Willberg, J., Rautava, J., & Laine, H. K. (ei pvm.). Binary- and Three-Tiered Oral Epithelial Dysplasia Grading System and Malignant Transformation. *Oral Diseases*, n/a(n/a). <https://doi.org/10.1111/odi.15334>

which has been published in final form at

DOI <https://doi.org/10.1111/odi.15334>

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ORIGINAL ARTICLE

Cancer and Potentially Malignant Disorders

Binary- and Three-Tiered Oral Epithelial Dysplasia Grading System and Malignant Transformation

 Riikka Ellonen^{1,2} | Jetta Kelppe³ | Jaana Hagström^{2,3,4} | Auli Suominen⁵ | Jaana Willberg^{1,2,6} | Jaana Rautava^{2,3,7} | Hanna K. Laine^{2,7}

¹Department of Oral and Maxillofacial Diseases, Turku University Hospital, Turku, Finland | ²Department of Oral Pathology and Radiology, University of Turku, Turku, Finland | ³Department of Pathology, HUSLAB, Helsinki, Finland | ⁴Translational Cancer Medicine Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland | ⁵Department of Community Dentistry, University of Turku, Turku, Finland | ⁶Department of Pathology, Turku University Hospital, Turku, Finland | ⁷Department of Oral and Maxillofacial Diseases, Clinicum, University of Helsinki, Helsinki, Finland

Correspondence: Hanna K. Laine (hanna.k.laine@helsinki.fi)

Received: 12 November 2024 | **Revised:** 28 February 2025 | **Accepted:** 25 March 2025

Funding: The authors received no specific funding for this work.

Keywords: binary grading system | dysplasia | malignant transformation rate | oral squamous cell carcinoma | three-tiered grading system

ABSTRACT

Objectives: Oral epithelial dysplasia (OED) can be graded histopathologically by using a binary- or three-tiered grading system. This study aimed to analyze and compare the prognostic value of the two systems in a large single-institute material.

Materials and Methods: The study was a retrospective histopathological re-evaluation analysis of 612 OEDs over 29 years at the Institute of Dentistry, University of Turku, Turku, Finland. OED patients who later developed squamous cell carcinoma (OSCC) were identified from the Finnish Cancer Registry database.

Results: Altogether, the mean age of 612 OEDs patients was 59.9 years. The male:female ratio was 0.67. According to the original three-tiered diagnosis, 67.7% of the samples were mild dysplasia, 28.7% moderate dysplasia, and 3.6% severe dysplasia cases. With binary-tiered diagnosis, low-grade dysplasia 84.1% was more common than high-grade dysplasia 15.9%. The malignant transformation rate was 7.8%. Regarding oral SCC development, no difference was found between the grading systems in predicting the malignant progression ($p=0.060$).

Conclusions: Both binary- and three-tiered grading systems of dysplasia classification had similar predictive value for malignant transformation.

1 | Introduction

Risk of malignant transformation of oral potentially malignant disorders (OPMDs) is assessed by combining clinical features of the lesion and the individual concerned, as well as histopathological grading of oral epithelial dysplasia (OED) (Speight et al. 2018; Odell et al. 2021). OED indicates a risk for malignant transformation towards oral squamous cell carcinoma (OSCC) (Warnakulasuriya et al. 2008). Histopathological features of OED are well known

(Kramer et al. 1978) although grading of dysplasia is criticized for terminology, definition, subjectivity, and lack of predictive value (Pindborg et al. 1985); (Karabulut et al. 1995); (Abbey et al. 1995). Grading of OED is not an exact science since grading systems are artificial constructs without knowledge of the underlying process (Odell et al. 2021) and it is subjective in nature (Mahmood et al. 2022); (Hankinson et al. 2024). The current criteria on OED classification have been published in 2022 by the World Health Organization (WHO) (Muller and Tilakaratne 2022).

Journal Name	ODI
Manuscript No.	15334
WILEY	
No. of pages: 8	Dispatch: 28-3-2025
PE:	CE:

1 Traditionally, OED has been graded in three categories by in-
2 creasing severity: mild, moderate, and severe (Warnakulasuriya
3 et al. 2008); (Kujan et al. 2006). The binary grading system,
4 proposed by Kujan et al. (Kujan et al. 2006) in 2006, divides
5 dysplasia into low-grade and high-grade dysplasia. Low-grade
6 dysplasia has fewer microscopic changes, and high-grade dys-
7 plasia has at least four architectural features and five cytolog-
8 ical features. The binary grading system aims to increase the
9 objectivity of histopathological grading (El-Naggar et al. 2017);
10 (Kujan et al. 2006). According to two recent studies, the binary
11 grading system could effectively determine malignant potential
12 by improving interobserver agreement over the three-tiered
13 grading system (Yan et al. 2020); (Khoury et al. 2022). Distinct
14 diagnosis could reduce the risk of malignant transformation by
15 improving efficient clinical management (Mehanna et al. 2009);
16 (Stojanov et al. 2024). Speight et al. (Speight et al. 2018) have
17 shown that severe/high-grade OED is associated with a higher
18 risk of malignant transformation in OPMDs than mild/moderate/
19 low-grade OED. Histological biomarker could be the ideal
20 way of identifying different prognostic groups among OEDs
21 (Tilakaratne et al. 2011); (Speight et al. 2018).

22
23 The aim of this retrospective study was to analyze and compare
24 whether the binary grading system of OED could have more
25 prognostic value compared to the three-tiered grading system in
26 assessing the risk of malignant transformation of OED in a large
27 single institute material from Finland with a long follow-up time.

2 | Materials and Methods

2.1 | Patients

28
29
30 Altogether, 922 patients with a histopathological diagnosis of
31 OED were retrieved from the registry of the Department of Oral
32 Pathology and Radiology, Institute of Dentistry, University of
33 Turku, Turku, Finland between the years 1982 and 2011. There
34 were three inclusion criteria: (1) OED as a histopathological diag-
35 nosis, (2) location in the oral cavity or lip mucosa, and (3) a refer-
36 ral letter with a Finnish social security number. Exclusion criteria
37 were concurrent carcinoma (or carcinoma in situ, a diagnosis used
38 before 2017) or samples that could not be diagnosed because of
39 poor quality. We have previously published a sub-analysis of this
40 cohort (Nevanpää et al. 2022). After exclusion, 612 patients were
41 re-evaluated. Clinical information of the patients and their oral
42 lesions (sex, age, habits, time of diagnosis, location, simultaneous
43 histopathological diagnosis such as candidiasis, ulcer, or lichenoid
44 inflammation) was collected from the referral letters. Location of
45 a lesion on oral mucosa was categorized according to the func-
46 tion and histology: lining mucosa (cheek mucosa, floor of mouth),
47 masticatory mucosa (palate, gum/alveolar mucosa), or specialized
48 mucosa of the tongue. Lip mucosa was separated from other lining
49 mucosa as a fourth group to rule out possible imprecise informa-
50 tion concerning the lip by clinician.

2.2 | Samples

51
52
53 Many patients had several samples with OED diagnosis
54 during the study period. The timewise first biopsy sample
55 from each patient was included in the study. If a patient had

several biopsies taken under the same timewise first visit with
the same sample identification number, the most severe OED
was chosen.

2.3 | Histopathological Diagnosis

At the time of original diagnosis, the OED grading followed
a three-tiered grading system according to the WHO guide-
lines (Warnakulasuriya et al. 2008; Kujan et al. 2006). In the
re-evaluation, two oral pathologists (J.K. and H.L.) graded the
samples histologically according to the current WHO guidelines
on a binary grading system (Muller and Tilakaratne 2022). Re-
evaluation was performed individually in a blinded manner. In
case of discrepancy in grading, the samples were re-analyzed by
a third oral pathologist (J.H.) followed by discussion until con-
sensus. Only so-called conventional dysplasias were included in
this study.

2.4 | Malignant Transformation

OSCC patients were identified from the Finnish Cancer
Registry (FCR) (decision no. THL/1475/5.05.00/2018) by their
Finnish social security number. ICD codes C00 and C02-C06
were considered as OSCC in this study. The follow-up ended
on 31 December 2017. To exclude unrecognized concurrent
carcinoma, the OSCCs that developed within 6 months after
the timewise first OED diagnosis were not included in the fol-
lowing analysis.

2.5 | Ethical Perspectives

This study was retrospective and registry-based, meaning no
patient was contacted during the study. The study protocol
was approved by the Ethics Committee of the Hospital District
of Southwest Finland (ETMK Dnro: 811180112019; 324) and
Statistics Finland, the Finnish Cancer Registry, and the Institute
of Dentistry, University of Turku as a registry holder. Patient
consent was waived by the Ethics Committee of the Hospital
District of Southwest Finland (ETMK Dnro: 811180112019; 324).

2.6 | Statistical Analysis

IBM SPSS Statistics for Windows, version 27.0 (IBM Corp.,
Armonk, NY, USA) was used to do the statistical analysis.
The results obtained are considered significant at $p < 0.05$.
Descriptive variables were calculated as percentages and con-
tinuous variables as means with standard deviation. The rig-
orous statistical method with valid assumptions was selected.
Statistical differences were tested using Chi-square (sex, age,
and smoking), Fisher's exact test or likelihood ratio test (binary-
and three-tiered grading system, location, cancer development),
the Joncheere-Terpstra test (time to OSCC), and Mann-Whitney
U-test (between binary- and three-tiered grading system in de-
veloping cancer) and one-way ANOVA (time to malignant trans-
formation). Kaplan-Meier curves and Log-rank test were used
to assess risk and kappa to interobserver agreement between
binary- and three-tiered grading systems.

3 | Results

3.1 | Patients

Altogether, 612 patients with OEDs fulfilled the inclusion criteria. All patients had a minimum of 6 years follow-up, mean 70.3 months. Follow-up time was 0.7–29.0 years, mean 5.9 years, SD=5.9. With original routine histopathological diagnosis by the Department of Oral pathology and radiology, University of Turku, Turku, Finland, there were 612 samples categorized as 394 (67.7%) mild dysplasia, 167 (28.7%) moderate dysplasia, and 21 (3.6%) severe dysplasia cases. In addition, 30 (4.9%) cases were diagnosed only as dysplasia without a specific subcategory. These cases were named dysplasia not otherwise specified (dysplasia NOS).

3.2 | Pathological Re-Evaluation

In the pathological re-evaluation of the OEDs, 472 (77.1%) samples fulfilled dysplasia criteria (El-Naggar et al. 2017; Muller and Tilakaratne 2022). Of these, 397 (84.1%) were low-grade dysplasia and 75 (15.9%) high-grade dysplasia.

3.3 | Comparison of Three-Tiered Grading System to Binary Grading System

We compared a three-tiered grading system to a binary grading system. The division between the binary and three-tiered grading systems is shown in Table 1. Analyzing differences with Fisher's exact test in the division of the three-tiered grading system to high- and low-grade dysplasias showed no statistical difference ($p=0.060$).

Majority of OED cases (91.3%) had some additional histopathological diagnosis, such as hyperkeratosis, signed out in the original routine examination. Besides OED diagnosis, the three most interesting additional diagnoses were of candidiasis in 10.0% of the cases, lichenoid inflammation in 7.2%, and ulcer in 17.4% of the cases. High-grade dysplasia had simultaneous candidiasis, lichenoid inflammation, and ulcer in 14.9%, 14.7%, and 19.5% of cases, respectively. Low-grade dysplasia had simultaneous candidiasis, lichenoid inflammation, and ulcer in 10.1%, 7.3%, and 16.6% of cases, respectively.

TABLE 1 | Comparison of three-tiered grading system to binary grading system.

	Low grade dysplasia	High grade dysplasia	Total
Dysplasia NOS	20 (5.0%)	4 (5.3%)	24 (5.1%)
Mild dysplasia	251 (63.3%)	36 (48.0%)	287 (60.8%)
Moderate dysplasia	114 (28.7%)	30 (40.0%)	144 (30.5%)
Severe dysplasia	12 (3.0%)	5 (6.7%)	17 (3.6%)
Total	397	75	472

3.4 | Sex and Age

Of the patients, 190 were men (40.3%) and 282 (59.7%) women. The mean age was 59.9 (range 15–94, SD 14.0) years. The mean age of men and women was 56.1 and 62.4 years, respectively. Low-grade dysplasia was more common among women (242, 61.3%) than in men. In Fisher's exact test analysis, no statistically significant difference of grades was found between genders ($p=0.30$).

There were 38 (9.6%) low-grade dysplasia and seven (9.3%) high-grade dysplasia in patients younger than 40 years. There were two patients under the age of 20 years; these both were categorized under mild dysplasia. Patients ≥ 60 years had significantly more high-grade dysplasia compared to the two younger age groups, 40–59 years and under 40 years ($p=0.016$) (Figure 1).

3.5 | Location

Of OEDs, 30.3% of cases had precise location information available in the referral letters. The most common location of low-grade dysplasia was mobile tongue (96/143, 67.1%) followed by buccal mucosa (59/143, 41.3%), floor of mouth (21/143, 14.7%), lip (19/143, 13.3%), palate (9/143, 6.3%), and gum/alveolar mucosa (7/143, 4.9%). Within high-grade dysplasia, the most common location was mobile tongue (22/50, 44.0%) followed by lip (8/50, 16%), buccal mucosa (8/50, 16%), floor of mouth (6/50, 12%), palate (3/50, 6%), and gum/alveolar mucosa (3/50, 6.0%). Grading of dysplasia in a binary grading system and its relation to different locations (mobile tongue, buccal mucosa, floor of mouth, lip, palate, gum/alveolar mucosa) did not show statistical significance between locations (likelihood ratio test $p=0.20$).

3.6 | Transformation to OSCC

Forty-one patients of all 612 patients (6.7%) developed OSCC. Of these, 25 (61.0%) were women and 16 (39.0%) were men.

When considering only patients with OED diagnosed in the pathological re-evaluation of the current study, 37 of 472 (7.8%) developed OSCC. Of the 37 OSCC cases, 7 (18.9%) transformed from high-grade dysplasia and 30 (81.1%) from low-grade dysplasia. Of the no-dysplasia cases, three of 140 (2.1%) developed OSCC.

Of OSCC cases in the re-evaluation group, there were 22 (59.5%) women and 15 (40.5%) men. The mean age of the patients was 57.0 years (range 27.7–79.9, SD 15.7). Patients <40 years, five of 62 (8.1%) developed OSCC. There was no increased risk for OSCC development for younger patients (<40 years) ($p=0.30$). The mean time of malignant transformation from low-grade dysplasia to OSCC was 5.4 years (SD 6.1) and for high-grade dysplasia, 5.5 years (SD=3.6). Figure 2 shows the distribution of OSCC development times in binary- and three-tiered grading systems. There was no statistical difference between OSCC development times between three-tiered and binary grading systems.

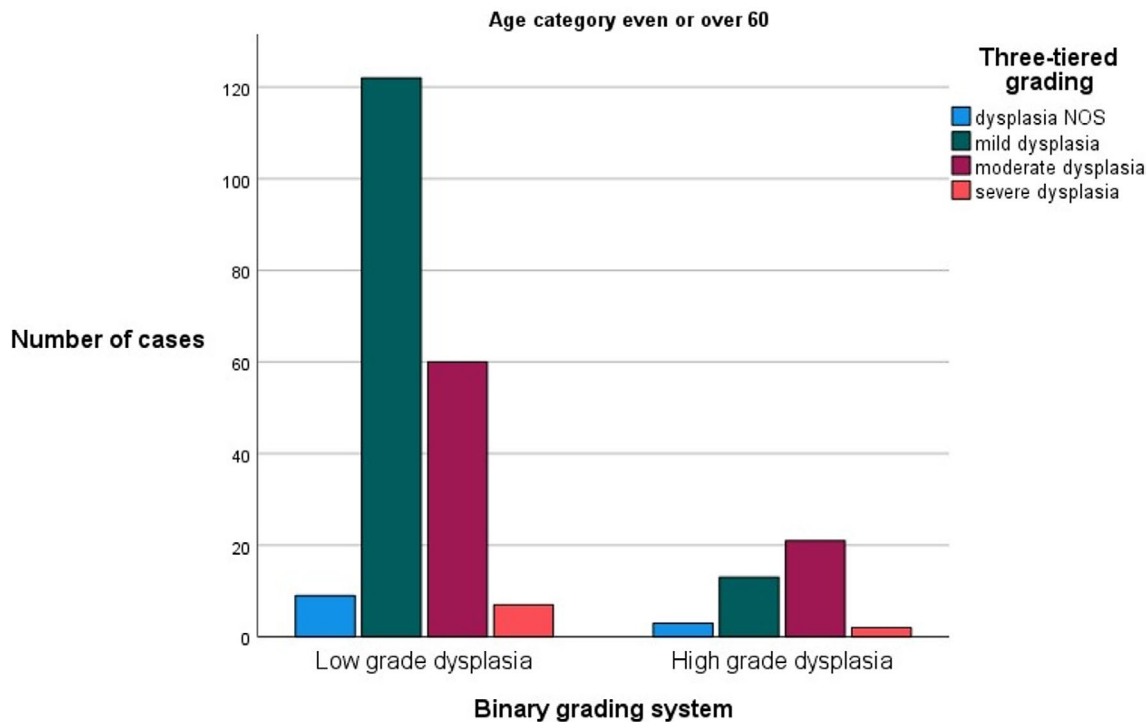


FIGURE 1 | Distribution of binary- and three-tiered grading systems of oral epithelial dysplasias of patients even or over 60 years old.

Most OSCCs occurred in mobile tongue (18/37, 48.6%) and in lining mucosa (buccal mucosa, floor of mouth) (7/37, 18.9%). No OSCC developed in lip or masticatory mucosa (palate, gum/alveolar mucosa). OSCC occurred in the same site as OED in 45.9% (17/37) of the carcinoma cases and in a different site in 21.6% (8/37) of the cases. In five of these eight patients, the OED was located on the tongue, but the OSCC developed on the other site of oral mucosa, and three vice versa.

3.7 | Smoking, Alcohol Consumption, and Additional Histopathological Diagnoses

Information on smoking was available for 116 of 472 (24.6%) OED patients. Of OSCC patients, 13.5% (5/37) were current or former smokers. There was no statistical difference between current or former smokers in the development of OSCC ($p=0.70$). None of the referral letters had information on snuff use available. Snuff use is prohibited in Finland.

Information of alcohol consumption was available for 20 of 472 (4.2%) OED patients. Of OSCC patients, only one of 37 (2.7%) patients was a moderate or heavy user of alcohol. Statistical difference was not seen in the occurrence of OSCC between current or former smokers.

Of the 37 OSCC patients, 32 (86.5%) had an additional histopathological diagnosis. There were additional diagnoses of candidiasis in one of the 37 (2.7%) cases, lichenoid inflammation in two (5.4%), and ulcer in four (10.8%) cases. High-grade dysplasia cases had no simultaneous candidiasis or lichenoid inflammation, but ulcer was diagnosed in one (14.3%) case. Of low-grade dysplasia, one case had simultaneous candidiasis (2.7%), two had lichenoid inflammation (5.4%) and three had ulcer (8.1%).

These additional histopathological diagnoses did not associate with an increased risk of OSCC development ($p=0.50$).

4 | Discussion

We compared the binary and three-tiered grading system of OED in a large single institute material from Finland with a long follow-up of 29 years. Both binary and three-tiered grading systems demonstrated similar prognostic accuracy. Therefore, we suggest in the light of this study that the binary grading system should be used for OED diagnostics, as it has been stated to be a more objective method for assessing OEDs (Khoury et al. 2022; Yan et al. 2020).

Within the binary system, OSCC development was more likely to occur in the group of low-grade than in high-grade dysplasia. The unexpected finding of the transformation rate in the group of low-grade dysplasia suggests that traditional grading systems may not adequately capture the complexity of malignant transformation risk. Histopathological analysis today is one feature in clinical decision making with oral potentially malignant lesions. Even low-grade dysplasias can progress to SCC in short periods. Therefore, Novack and his coworkers (Novack et al. 2023) have proposed that staining could help identify lesions at high risk for malignant transformation. They noticed that in the case of abnormal p53 staining in OED, the lesion was more likely to progress to invasive SCC than p53 wild-type oral epithelial dysplasia.

Previously, high-grade dysplasias have been shown to have a worse outcome compared to low-grade dysplasias (Speight et al. 2018; Gilvetti et al. 2021; Ho et al. 2012; Spielmann et al. 2010). In this study, low-grade dysplasias had more malignant transformation than high-grade dysplasias. In a

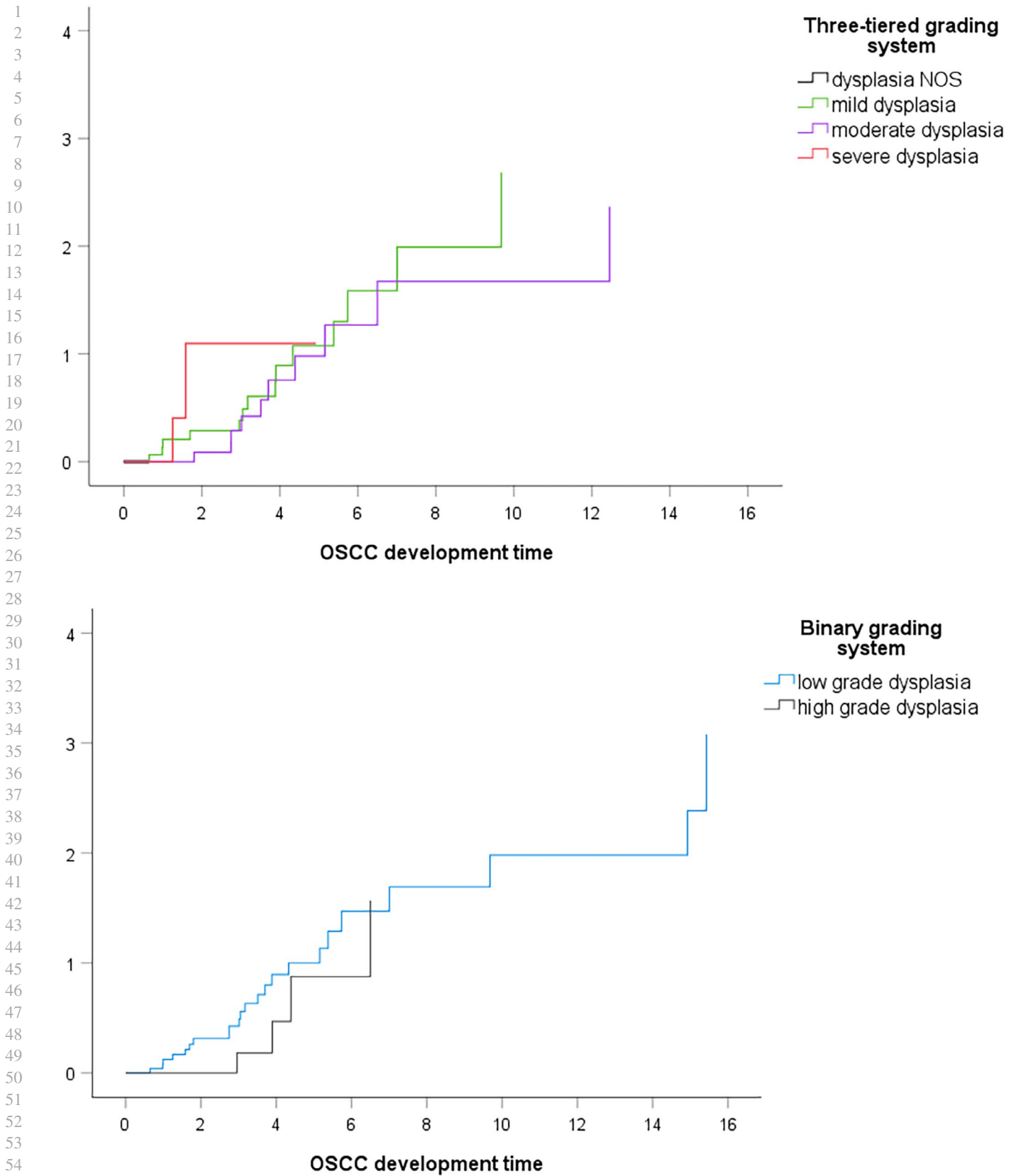


FIGURE 2 | Hazard graphs of binary- and three-tiered grading systems regarding OSCC development time.

meta-analysis, Yan et al. showed that the binary system could effectively determine malignant potential, with improved interobserver agreement compared to the three-tiered system

(Yan et al. 2020). However, Sperandio et al. have shown that the three-tiered system could present superior prognostic value to the binary system since risk assessment could improve if

intermediates such as borderline lesions get double-grading from both systems. This could help the clinician if evaluation is done by both grading systems (Sperandio et al. 2023).

In the current study, the mean time of malignant transformation from low-grade dysplasia to OSCC was 5.4 years and for high-grade cases 5.5 years without statistical significant difference. OSCC development from OED is previously described to be 3.8–4.2 years in high-grade dysplasia (Gilveti et al. 2021). Low-grade dysplasia has been described to develop to OSCC in 6.2 years (Yan et al. 2020). Interestingly, in our study, this was 5.4 years. Longer follow-up time of our study could be the reason for the difference in OSCC development time.

Site is important when considering the risk of malignant transformation of an individual lesion. In our study, OSCC occurred predominantly on the mobile tongue and secondly on lining mucosa (buccal site or floor of the mouth) as a functional site. The mobile tongue, especially its side, is well known as a risk site for malignant transformation (Jäwert et al. 2021; Pimenta-Barros et al. 2024).

Concurrent diagnoses and risk factors such as tobacco, smoking, and heavy alcohol use are well-known risk factors for OED and OSCC (Odell et al. 2021). In the current study, these did not show significance in the risk evaluation of OEDs. However, there was a lack of information on referral letters on these lifestyle factors. Smoking was available only for 25% OED patients and is a limitation of our study. The information on alcohol consumption was available for even fewer patients, only for 4% OED patients. Of OSCC patients, 3% were using alcohol moderately or heavily. Interestingly, Speight and co-workers have stated that there is not much evidence of the role of alcohol in the progression of OEDs (Speight et al. 2018). The malignant transformation remains poorly understood due to the complexity of the analysis of OED and numerous genetic changes (Odell et al. 2021). In our study, it is crucial to interpret the results of these etiological factors with caution due to missing information. The true atypia and complicating factor of inflammation need also to be taken into account since inflammation might hamper the diagnostics of the pathological diagnosis of OED (Gerardo et al. 2020).

Oral cancer as well as OED typically appears in patients over 40 years of age. Our study showed that there were 10% of low-grade dysplasia and 10% of high-grade dysplasia with patients younger than 40 years. There was even one patient of 16 years of age with OED who was diagnosed later as oral squamous cell carcinoma developing from mild OED. The etiology of OED with these younger patients may have a role of genetic factors. There are up to 20 familial cancer syndromes that may potentiate cancer development in the oral cavity, and people born with inherited genetic predispositions develop malignancies at a younger age and with a relatively high frequency (Warnakulasuriya et al. 2020).

We found significantly more high-grade dysplasia cases in the age group ≥ 60 years old compared to other age groups. Mahmood et al. (Mahmood et al. 2022) have shown similar results among older patients. In the literature, this has been related to genetic alterations and chronic exposure to environmental risk factors in aging (Gupta et al. 1980; Ranganathan and Kavitha 2019).

Aging increases the risk of cancer by targeting specific p53 gene codons in a carcinogenic pattern (Rodin and Rodin 2005).

Controversial to our results, others have found candidiasis infection more frequent in high-grade OEDs (Hongal et al. 2015; McCullough et al. 2002; Odell et al. 2021). In the systematic review by Shukla et al., candidiasis infection was shown to be a possible promoter of dysplastic changes of oral mucosa (Shukla et al. 2019). In addition, candidiasis might affect cancer-associated signaling pathways, thus acting as a cancer promoter (McCarthy et al. 2021). In the current study, 15% of high-grade dysplasia had simultaneous candidiasis, but only one case developed to OSCC.

In the current study, not all samples were re-evaluated as dysplastic. This highlights the difficulty of reproducibility of dysplasia grading. Interobserver variability exists especially in low-grade lesions where inflammatory processes and reactive processes are included (Khoury et al. 2022; Abbey et al. 1995; Warnakulasuriya et al. 2008; Ranganathan et al. 2020). According to Stojanov et al., misdiagnosing OED and instead diagnosing it as lichenoid inflammation might quite easily happen in low-grade dysplasia (Stojanov et al. 2024; Márquez et al. 2023). One new entity is differentiated dysplasia. WHO mentions it in the 2022 classification. In the current study, this new entity was not included in the study. However, the 140 excluded dysplasias without conventional dysplasia, the pathological re-evaluation may, at least partly, represent differentiated dysplasias. This highlights the fact that we do not have a single consistent histopathological marker helping the clinicians work with these lesions. Careful follow-up by the clinician as well as by the patient him/herself still has the major role in early diagnosis of oral cancer. It is important to notice that 2% of nodysplasia cases in the re-evaluation developed OSCC. Therefore, all oral mucosal lesions must be followed up, not only the ones with dysplasia.

In the current study, our strength is a large material of OED cases from a single institute with a long follow-up of 29 years. As a limitation, referral letters for histopathological analysis had only limited information available on smoking or alcohol consumption, which both are proved to act as etiological factors in OSCC development.

5 | Conclusions

In this large single institute cohort of 29 years, the binary- and three-tiered grading systems of OED grading had similar predictive value for malignant transformation.

Author Contributions

Riikka Ellonen: writing – original draft, data curation, formal analysis, methodology, visualization, investigation, resources. **Jetta Kelppe:** writing – review and editing, methodology, formal analysis. **Jaana Hagström:** writing – review and editing, methodology, formal analysis. **Auli Suominen:** software, formal analysis, methodology. **Jaana Willberg:** supervision, methodology. **Jaana Rautava:** project administration, supervision, writing – review and editing, methodology, formal analysis, conceptualization, investigation, funding acquisition.

Hanna K. Laine: supervision, project administration, writing – review and editing, methodology, formal analysis, conceptualization, investigation, resources, validation.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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