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S2k guideline "Diagnostics and management of precursor lesions of oral squamous cell carcinoma in dental and oral medicine"

Overview: The update of the guideline on "diagnostics and management of precursor lesions of oral squamous cell carcinoma in dental and oral medicine" began in 2017 and was finalized in April 2020 after a total of 3 formal consensus processes. It was coordinated by the German Society of Dental and Oral Medicine (DGZMK) and the German Society for Oral and Maxillofacial Surgery. Specifically, the guideline updates the knowledge and recommendations, particularly the following aspects:
– the classification of potentially malignant oral lesions considering the updated WHO classification of 2017
– special status of proliferative verrucous leukoplakia
– definition of "suspicious" lesions under observation of clinical evidence of a malignant transformation
– specific designation of examinations, whose significance is not supported with reliable study data
– topical corticoid therapy of lichen, especially intralesional therapies
Furthermore, the existing recommendations were updated and complemented by statements and new recommendations.

Keywords: precursor lesion; dental and oral medicine; malignant transformation; early detection; screening; oral mucosa; WHO classification

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WHO 2017: Dysplasia	WHO 2005: Dysplasia	Ljubljana classification squamous intraepithelial lesions (SIL)	Squamous intraepithelial neoplasia (SIN)	Reduced squamous intraepithelial neoplasia (SIN)
–	squamous hyperplasia	(simple) squamous hyperplasia	–	
low grade dysplasia	low grade dysplasia	basal and parabasal hyperplasia	SIN I	SIN: low risk
moderate dysplasia	moderate dysplasia	atypical hyperplasia (risk epithelium)	SIN II	SIN: high risk
high grade dysplasia	high grade dysplasia		SIN III	
carcinoma in situ	carcinoma in situ	carcinoma in situ		
invasive carcinoma	invasive carcinoma			

*Since both moderate dysplasia and high grade dysplasia are considered "high risk" lesions, the graduation can be modified to a binary structure "low grade" and "high grade" (with "high grade" including moderate and high grade dysplasia)

Overview 1 Synopsis of classifications of potentially malignant oral lesions [6, 7, 10, 25]

Introduction

It's the guidelines' aim to record the current state of knowledge for a relevant problem in health care and if possible, draft key statements in the form of clear recommendations for action. For this, regular updates are necessary in order to keep up with the development of scientific knowledge. Having said this, the update of the guideline "diagnostics and management of precursor lesions of oral squamous cell carcinoma in dental and oral medicine" was started in 2017 and finalized in April 2020. It was carried out by the German Society for Dental and Oral Medicine (DGZMK) and the German Society for Oral and Maxillofacial Surgery. The update of the guideline was added to the list of prioritized topics of the task force of DGZMK, BZÄK and KZBV, which consisted of representatives of DGZMK, KZBV and BZÄK.

The authors of the guideline conducted current literature research (Medline) until 2018 to draft the recommendations and background text and included the relevant literature in the guidelines. Based on the existing guidelines, the coordinators revised the document in the first step and added current literature. Simultaneously, certain wordings were clarified that had led to misunderstandings in the past, and a formal division between recommendations and statements was included. The referencing of other guidelines was also updated.

This draft was the basis of a formal Delphi method with two Delphi rounds and a conclusive consensus conference with the participation of elected representatives of professional societies on 23.01.2019 in Cologne (see Tab. 1) under methodical moderation of AWMF. Within this consensus conference, the key statements and additions in the context of literature were discussed and a formal and structured consent added to the methodology of a nominal group process. Because this is an S2k guideline, a more detailed evaluation of studies in the sense of an evidence grading or even weighting and synthesis of study results did not take place.

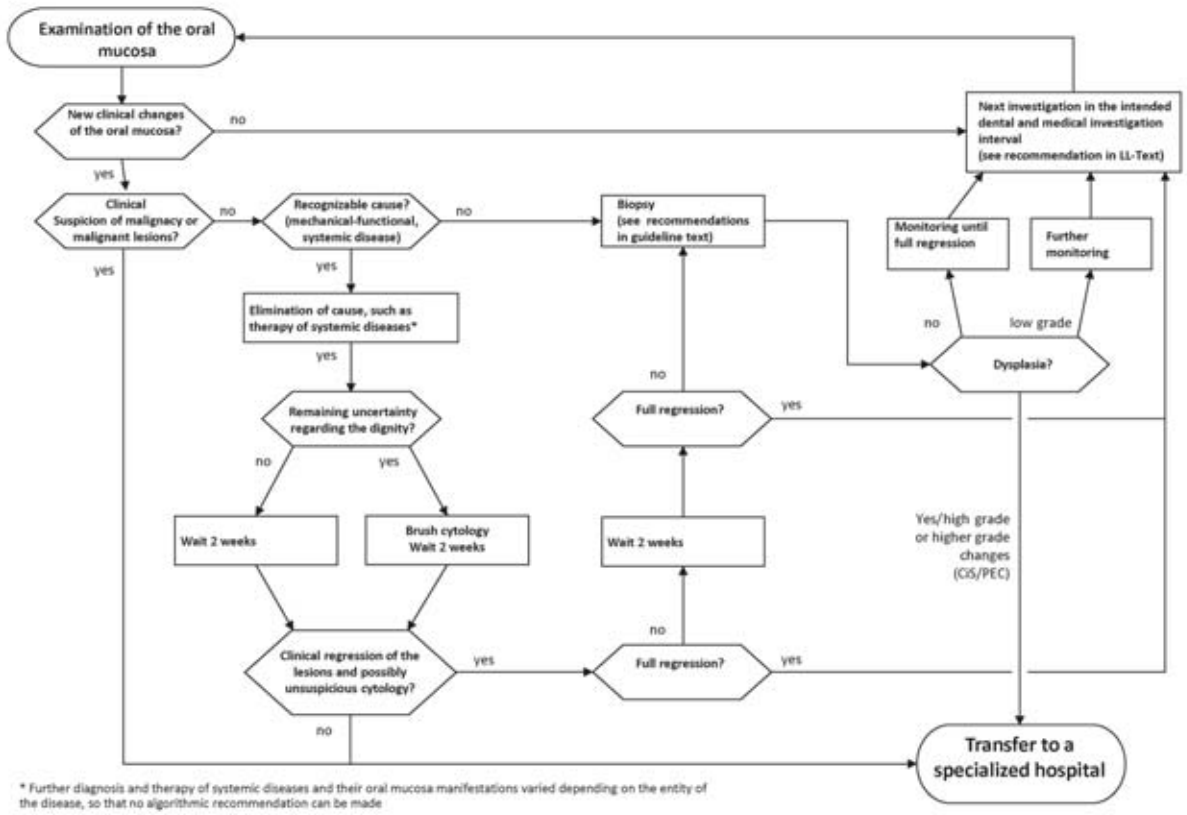
Updated precisely, the guideline specifies the current knowledge and recommendations, particularly the following aspects:

- classifications of potentially malignant oral lesions regarding the updates WHO classifications of 2017
- special status of proliferative verrucous leukoplakia
- definition of "suspicious" lesions under observation of clinical evidence of a malignant transformation
- specific designation of examinations, whose significance is not supported with reliable study data
- topical corticoid therapy of lichen ruber mucosa, especially intralesional therapy
- recommendations

The state of research and the decision criteria of recommendations were renewed in form of background texts as in the previous version, which were included in the extended version of the guideline. Since these texts create references to relevant literature, they are displayed here for information.

Classifications of potentially malignant oral lesions in consideration of the upgraded WHO classification of 2017

In the current WHO classification of head and neck tumors 2017 [7], mostly classification of dysplasia degrees are used. However, the term squamous intraepithelial neoplasia (abbreviated: SIN) will continue to be used as a synonym of potentially malignant lesions (previously: oral precursor lesions) of squamous cell carcinoma. The potentially neoplastic character of the lesion is depicted in



(Overview 1, Fig. 1 and Tab. 1: K. Hertrampf, M. Kunkel)

Figure 1 Algorithm for the guideline "diagnostics and management of precursor lesions of oral squamous cell carcinoma in dental and oral medicine"

the nomenclature. In the following, the term of potentially malignant oral lesions classification (2017) instead of precursor lesions and other terms is used according to WHO (precancerous condition, precancerous lesion, potentially malignant lesion, precursor lesion etc.).

Compared to earlier versions of the WHO classification, a reduction of degrees of dysplasia is introduced in the form of a binary classification. Ultimately, the three traditional degrees of dysplasia are reduced to a "low grade" group and a "high grade" group, which essentially corresponds to the clinical risk assessment and signals a distribution into "low risk" SIN and "high risk" SIN. In earlier nomenclature, high grade intraepithelial neoplasia (SIN 3) included the carcinoma in situ of earlier classifications (carcinoma risk of 90 %) [3, 5, 15, 27], (see overview 1).

Special status of proliferative verrucous leukoplakia

The proliferative verrucous leukoplakia (PVL) has a special status, because the morphological degree of dysplasia does not correlate with the clinical risk potential. Even though low degrees of dysplasia are typically found in PVL or can be missing completely, a highly malignant transformation rate (about 70 %) and consecutively high tumor-related mortality is expected with this entity.

Definition of "suspicious" lesions while describing clinical features of a malignant transformation

The recommendations for action are based on the fact that oral lesions that are evaluated as "suspicious" for malignant transformation. Apart from the chronological development (persistence of a lesion for more than 2 weeks) the following clinical criteria should be regarded as indicators suggestive of a malignant transformation, specifically:

- newly occurred and of unknown duration
- thick hyperkeratosis
- inhomogeneity
- erosion
- bleeding on contact or light mechanical stress
- missing cause
- pathological vascular dilation/ vessels

The algorithm for complete examination of the oral mucosa was updated (Fig. 1).

Examinations, whose significance is not supported with reliable study data:

The description of research methodology was upgraded and newly structured. Specifically, a group of examinations is designated whose significance is not supported with reliable study data.

Professional societies involved/ Organizations	Abbreviation	Elected representatives
Working Group for Oral and Maxillofacial Surgery	AGOKI	Prof. Dr. A. M. Schmidt-Westhausen
Working Group Oral Pathology and Oral Medicine	AKOPOM	Prof. Dr. Dr. U. Müller-Richter
Federal Association of German Oral Surgeons	BDO	Prof. Dr. J. Jackowski Prof. Dr. T.M. Remmerbach
Federal Association of Dentists	BZÄK	Dr. J. Beck
Professional Association of German Pathologists	BDP	§)
German Dermatological Society	DDG	Prof. Dr. F. Kiesewetter
German Society for Otorhinolaryngology, Head and Neck Surgery	DGHNO-KHC	Prof. Dr. J.P. Klußmann Prof. Dr. C. Wittekindt (deputy)
German Society of Implantology	DGI	Prof. Dr. F. Schwarz
German Society for oral and maxillofacial surgery	DGMKG	Prof. Dr. K. Hertrampf (coordination) Prof. Dr. Dr. M. Kunkel (mandate)
German Society of Peirodontology	DGPARO	PD Dr. C. Graetz
German Society of Pathology	DGP	§)
German Society for Dental Prosthetics and Materials Science	DGPro	Prof. Dr. H.-J. Wenz, MME
German Cancer Society (working group ENT and OMF-surgery in oncology)	DKG	Prof. Dr. J.P. Klußmann
National Association of Statutory Health Insurance Dentists	KZBV	Dr. J. Beck

§) The elected representative of the German Society of Pathology (DGP) and the Professional Association of German Pathologists (BDP) left the guideline group during the creation process. Both specialist groups were given the opportunity to comment on the finalized draft guideline and both approved.

Table 1 Listing of the professional societies involved/organizations and the elected representatives

Necessary examinations for therapy decisions:

- inspection: using a systematic examination procedure it is ensured that all relevant regions of the oral mucosa can be investigated and critically assessed
- palpation

Further investigations:

- review of causes of mechanical irritation
- sensitivity test of neighboring teeth to record odontogenic inflammatory causes
- determining periodontal parameters to record periodontal causes
- x-ray examination to record dental and osseous inflammatory causes
- examination of lymph node status to evaluate accompanying inflammatory reactions or to recognize the spread of the tumor
- sensitivity test (lingual nerve and mental nerve) to evaluate sensation of pain or to recognize the spread of the tumor

Helpful examinations in justified individual cases:

- swab for microbiological diagnostics
- virological diagnostics
- reviewing a reaction to dental materials

Examinations, whose significance is not supported with reliable study data:

- intravital staining with toluidine blue[a]
- visual tools
  - chemiluminescence and autofluorescence diagnostics[b]
  - narrow band imaging[c]

The background texts were updated to help explain.

a) Intravital staining with toluidine blue

Methods of intravital staining of the oral mucosa for specific emphasis of malignant lesions on basis of tolui-

dine blue have been described for more than 40 years. The basic principle postulated is the increased binding of the dye with DNA-affinity in tissues with higher cell conversion [19]. On a molecular level the association between chromosomal changes (e.g. 3p/9p LOH) and staining behavior of oral mucosa changes were shown [30].

The accuracy in clinical investigations is variable, there are values of 38–98 % for sensitivity and a range of 9–93 % for specificity [4, 19, 20]. Despite the long-term availability and a large number of literature notifications, only a few studies address the application of toluidine blue in order to detect oral mucosa lesions that have not already been previously recognized clinically [12]. In addition, more authors are critical of the low accuracy for potentially malignant oral lesions with a sensitivity of under 50 % [9, 16, 18].

Overall, the big effort involved with chairside application has prevented the clinical implementation of staining and the expansion of the methods and usage in dental practices. In literature, there is no data on the application in primary care. After more than five decades, a relevant development and expansion of the method is not to be expected.

b) Chemiluminescence and autofluorescence diagnostics

In the last few years, the procedures for chemiluminescence and autofluorescence diagnostics were examined as supportive visual tools in detecting potentially malignant oral lesions and oral carcinomas in different studies. In the process of the chemiluminescence source of light, the oral mucosa is pretreated with 1 % acetic acid. Possible modifications in the keratinization are supposed to show up in white and then stand out after subsequent treatment with toluidine blue. In autofluorescence diagnostics, dysplastic or neoplastic lesions are supposed to show up darker compared to healthy (green) oral mucosa, due to the loss of fluorescence. Koch et al. (2010) were able to show a high sensitivity of 93 % in a patient collective (N = 78) with conspicuous clinical mucosa lesions in the examination using autofluorescence diagnosis, however, the specificity was only at 13–17 % [11]. In the study of Mehrota et al. (2010) both visual methods came into effect and showed significantly worse results [17]. The procedure with autofluorescence showed a sensitivity of 50 % and a specificity of 38.9 % in 156 examined lesions. When applying chemiluminescence in 102 examined lesions, the sensitivity was at 0 and the specificity at 75.5 %. Further studies that investigated these procedures showed similar critical, unsatisfactory results [1, 2, 8, 21, 22]. The inhomogeneous and inadequate data shows no scientific basis for the application of either visual procedure in early detection of potential malignant oral lesions and oral carcinomas.

c) Narrow band imaging

Another visual method that was evaluated in studies for early detection of oral carcinomas and potentially malignant oral lesions in the last few years is the narrow band imaging from other areas of surface diagnostics in the oral cavity in studies. The method used two narrow-banded frequency domains (400–430 nm and 525–555 nm) in order to depict differences in vessel plexus instead of continuous frequency spectrum of white light. Yang et al. (2012 and 2013) showed a sensitivity of 96.3 % for the narrow band imaging using a patient collective of n = 317 and a specifity of 60.1 % compared to white light with 87 % sensitivity and 93.5 % specificity. However, the transferability of the results and a potential recommendation is only possible to a limited extent, because in studies from Asian countries, many lesions are buccal lesions, caused by the enjoyment of betel products and therefore many localisations for lesions were underrepresented [28, 29]. A systematic review from 2014 [26] came to the conclusion that this method has diagnostic potential, however, a statement for recommendation in the field of early detection is not possible due to the insufficient and inadequate data.

Topical corticoid therapy of mucosal lichen ruber, particularly intralesional therapy

Also the background text on measures of demarcation of inflammatory/irritating phenomenons was extended and specifically, the intralesional therapy with corticoid was included.

Local corticoid therapy

For a symptomatic lichen ruber the local treatment using steroids is the therapy of choice [13]. There is not enough evidence for a recommendation of a specific steroid therapy regarding the outcome of "pain reduction" [24]. This was also confirmed by the study of Liu et al. (2013) [14]. They could, however, determine a positive therapy effect of an intralesional therapy with betamethasone compared to therapy with triamcinolone in their randomized, controlled study regarding the outcome "recurrence of a lesion within three months".

Unresponsiveness to steroid application confirms the indication of a biopsy [23].

Recommendations

Since the key statements of the guideline are formulated in the recommendations, all recommendations of the guideline are written out in the following. An explanation of modifications was included when significant changes have been made to the previous version.

Recommendation 1:	
Within the recommended systematic examination of the oral cavity every 6 months it should be ensured that all regions of the oral mucosa, the lips and the neighboring tissues are critically investigated. When changes are observed, further diagnostics should take place.	**strong consensus**

Expert consensus

Recommendation 2:	
When the cause of mucosal changes is assumed, e.g. a mechanical irritation of inflammatory systemic disease, the cause should be eliminated first, and if necessary this includes treating the systemic disease	**strong consensus**

Expert consensus

Recommendation 3:	
In case of suspecting a manifested carcinoma, the patient should be refered immediately to introduce further diagnostics and therapy	**strong consensus**

Expert consensus

Recommendation 4:	
When suspecting a malignant transformation of the mucous membrane, a histological clarification should take place	**strong consensus**

Expert consensus

Recommendation 5:	
For a cytological diagnosis, the harvesting procedure should be done using brushes, because they can collect superficial as well as deeper cell layers	**strong consensus**

Expert consensus

Statement 1:	
There is not enough evidence for a recommendation regarding application of further technology in cytology (immunohistology, DNA cytometry etc.) in early recognition of oral precursor lesions.	**strong consensus**

Expert consensus

Recommendation 6:	
If a biopsy might not be representative of the whole lesion, a complete diagnostic excision should take place	**strong consensus**

Expert consensus

Recommendation 7:	
If a mucosal lesion is considered non-malignant and there is no need for an biopsy, nonetheless monitoring is intended since some uncertainty remains regarding the dignity of oral mucosa lesions, a brush cytology should be used	**consensus**

Expert consensus

Recently incorporated recommendation

Recommendation 8:	
In extended oral mucosa lesions, where a diagnostic excision would lead to a highly perioperative morbidity, an extensive brush biopsy is an alternative to multiple simultaneous biopsies.	**strong consensus**

Expert consensus

For extensive oral mucosal lesions with chronic progression (for example with a proliferative verrucous leukoplakia) there is the problem that on one hand, representative localisations (e.g. most advanced in tumor progression) can sometimes not be defined, and on the other hand, a complete diagnostic excision especially in cross-regional lesions can imply the perioperative morbidity of a tumor resection or is not technically feasible in multifocal lesion. In these rare cases, the large surface coverage of the brush biopsy (reduction of "sampling errors") must be weighted against the greater diagnostic accuracy of the excision biopsy (limited to the excised tissue).

Recommendation 9:	
It is possible to refrain from incision or excision biopsy when a regression of the lesion is noticeable within two weeks after elimination of an adequate cause*. In this case, the clinical control should be continued until complete regression, because a partial regression of malignant lesions can be feigned by overlapping inflammatory components	**consensus**

Expert consensus

Recommendation 10:	
A histological clarification (biopsy) should take place**, if there is a beginning regression in the first two weeks, but not a complete healing after two more weeks	**strong consensus**

Expert consensus

/The timeframe of recommendations 9 and 10 apply to patients where normal wound healing can be expected.*

Recommendation 11:	
According to prevailing opinion, lesions that are clinically homogeneous, and evaluated as histologically "low grade" (previously SIN I or low dysplastic) can be primarily monitored.	**strong consensus**
Lesions that are histologically classified als "high grade" (previously SIN II or III, or moderately or highly dysplastic) should be excised completely.	**consensus**

Expert consensus

Recommendation 12:	
When there is a discrepancy between the clinical appearance and the histological evaluation (for example. inhomogeneous leukoplakia without histological dysplasia), another histological review or a transfer for a second opinion/introduction of further diagnostics and therapy should follow	**strong consensus**

Expert consensus

Recommendation 13:	
After removal or monitoring of low grade dysplastic lesions an inspection interval of 6 months should be followed. In all other manifestations of dysplastic lesions, a check-up interval of 3 months should be followed.	**consensus**
Specific recommendations exist for mucosal lichen ruber for the necessity of constant monitoring. The check-up interval should not exceed four months.	**consensus**

Expert consensus

Recommendation 14:	
A check-up should always be recommended to the patient, independent from the type of therapy.	**strong consensus**

Expert consensus

Recommendation 15:	
In general, an outpatient treatment under local anesthesia is sufficient. A treatment in general anesthesia/sedation can be indicated depending on localisation or due to expected problems in co-operation of the patient (e.g. gag reflex), in patients with large overall extent of mucogingival measures, in manifested local risk factors or after consideration of these criteria based on the preference of the patient. In-patient treatment can be indicated in severe systemic diseases or particular surgery developments.	**strong consensus**

Expert consensus

There is additional information available in the form of a more detailed guideline report. The documents can be downloaded from the websites of the AWMF, BZÄK and the DGZMK. The next update is planned for 2025.

Conflict of interest

The authors state that there is no conflict of interest within the guidelines of the International Committee of Medical Journal Editors.

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