Using ROC analysis to confirm an algorithmically established diagnosis of lichen planus

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Abstract. The use of ROC analysis allowed the authors to determine cytogenetic criteria to confirm the diagnosis of lichen planus, obtained by selecting the most informative features and interpreting the micronucleus test in buccal epithelium, calculating their critical values, sensitivity and specificity for use as diagnostic tests. An increase in the number of cells with micronuclei in the lesion of lichen planus is a sign of genetic instability, which can trigger the process of their malignancy. Recognition of nuclear aberrations against the background of nuclear destruction makes it possible to diagnose lichen planus in patients.

1. Introduction
This early diagnosis of human diseases is an important task of modern medicine. In this regard, it is relevant to search for criteria for early diagnosis of diseases, including cancer. Currently, research is actively conducted to identify the influence of pathological processes on the frequency of cells' occurrence with core abnormalities in the buccal epithelium of a person, since it is a kind of "mirror" of the state of the entire body.

The criterion "number of cells with genetic abnormalities" can be used as a marker of malignancy in the early diagnosis of cancer, as well as in the detection of oncogenic factors. For example, many authors [1, 2] note an increased level of cells with micronuclei in patients with carcinoma and in a precancerous state.

The precursor of carcinoma is lichen planus of the oral cavity – a chronic inflammatory immune-dependent disease of the skin and mucous membranes with a characteristic lesion of the mucous membrane of the mouth, gums, tongue, and lips, so it is important to diagnose this disease as soon as possible. A micronucleus test of buccal epithelial cells can help with early diagnosis of lichen planus [3]. By identifying the frequency of violations in this disease and comparing them with those of healthy people, you can determine how high the risk of developing lichen planus is.

The authors previously [4] developed and implemented in clinical practice an algorithm for diagnosing lichen planus, which provides for two main modes of operation:

1) using the results of a micronucleus test in the buccal epithelium, which informs about the presence of red lichen planus in the patient, and further work related to determining the form of the disease and predicting the course depending on the form;

2) differential diagnosis of lichen planus, implemented using the Kohonen neural network, with diseases such as decubital ulcers with signs of hyperkeratosis, trophic ulcers with signs of...
hyperkeratosis, erosive leukoplakia, chronic lupus erythematosus, vulgar pemphigus, ulcerative-necrotic stomatitis, multiform exudative erythema, recurrent aphthous stomatitis, and then, when detecting lichen planus, the transition to the first mode.

Since the result of the micronucleus test in the buccal epithelium is not a specific sign of lichen planus, it was necessary to find evidence to confirm the presence of this disease in patients. In this regard, the aim of the work was to study the spectrum and frequency of nuclear abnormalities in buccal epithelium by patients with lichen planus to assess the diagnostic information content of the studied signs.

2. Materials and methods
The research was conducted at the Department of dentistry, Institute of additional professional education the Voronezh State Medical University named after N. N. Burdenko and the Department of genetics, Cytology and bioengineering medical and biological faculty of Voronezh State University.

An analysis of the occurrence of nuclear aberrations in buccal epithelial cells of 15 women aged 50 to 60 years, patients with lichen planus. 10 women of the same age group without this disease were selected as control group. The obtained materials were analyzed using a Laboval-4 microscope (Carl Zeiss, Jena). A total of 40 drugs were studied with the analysis of 45738 cells. Critical significance levels for statistical hypothesis testing: 0.05; 0.01; 0.001.

All violations captured during the preparations, were classified as follows:
1) cytogenetic indicators (microkernel, protrusion type "tongue" and "broken eggs);
2) indicators of the nucleus’ destruction (perinuclear vacuole, karyopyknosis, karyorhexis, karyolysis);
3) indicators of proliferation (notch).

For statistical data processing, we used the "STATISTICA 6.0" and "STADIA" software packages. The studied data were checked for compliance with the normal law using the Shapiro-Wilk test, which is applied for an initially unknown mean value and mean square deviation.

The frequency of occurrence of buccal epithelial cells with abnormalities in the subjects was compared using the nonparametric X-test of van der warden ranks. Analysis of variance was carried out using nonparametric criterion Kruskal-Wallis. To search for cytological indicators with diagnostic value, ROC analysis was used (MedCalc 17.1 program).

The possibilities of using ROC analysis in medicine are described in the work of S. G. Grigoriev and co-authors [5]. The name comes from signal processing systems.

The ROC curve (Receiver Operator Characteristic) is the curve that is most often used to represent binary classification results in machine learning. Since there are two classes, one of them is called a class with positive outcomes, and the second is called a class with negative outcomes.

The ROC curve shows the dependence of the number of correctly classified positive examples on the number of incorrectly classified negative examples. In the terminology of ROC analysis, the former is called a true positive set, and the latter are called a false negative set. In this case, it is assumed that the classifier has a certain parameter, varying which, one or another division into two classes is obtained. This parameter is often called a threshold or cut-off point (cut-off value). Depending on it, different values of errors of the I and II types will be obtained.

Two definitions are important: model sensitivity and specificity. They determine the objective value of any binary classifier. Sensitivity is the percentage of truly positive cases. Specificity – the percentage of truly negative cases that were correctly identified by the model.

For an ideal classifier, the ROC curve graph passes through the upper-left corner, where the percentage of true positive cases is 100% or 1.0 (ideal sensitivity), and the percentage of false positive examples is zero. Therefore, the closer the curve is to the upper-left corner, the higher the predictive power of the model is. On the contrary, the smaller the curve bends and the closer it is to the diagonal line, the less efficient the model is. The diagonal line corresponds to a "useless" classifier, i.e. the complete indistinguishability of the two classes.
When visually evaluating ROC curves, their relative positions indicate their relative effectiveness. The curve located higher and to the left indicates a greater predictive ability of the model. A peculiar method for comparing ROC curves is to estimate the area under the curves. Theoretically, it changes from 0 to 1, but since the model is always characterized by a curve located above the positive diagonal, it is usually said to change from 0.5 ("useless" classifier) to 1.0 ("ideal" model). The Euden index is the difference between the proportions of true positive cases in patients and false positive cases in individuals without the disease.

3. Results and discussion
As a result of the study using ROC analysis, it was found that for samples taken in the area of the teeth closing zone, none of the studied features has diagnostic value (the area under the curve is no more than 0.5). Taking into account the total number of violations, it is possible to diagnose a pathology with a sensitivity of 80% and a specificity of 60%, using the value 25.3‰ as the cut-off point.

For samples taken directly in the affected area, the greatest diagnostic value is the indicators of karyolysis, karyorexis, frequency of occurrence of perinuclear vacuoles, karyopyknosis (table 1).

| Indicator        | Area under the curve | Yuden Index | Sensitivity % | Specificity % | Pointcut-offs |
|------------------|----------------------|-------------|---------------|---------------|---------------|
| Karyolysis       | 1.0                  | 1.0         | 100.0         | 100.0         | 0.9           |
| Karyorhexis      | 1.0                  | 1.0         | 100.0         | 100.0         | 1.1           |
| Perinuclear vacuole | 0.98               | 0.9         | 90.0          | 100.0         | 7.0           |
| Karyopyknosis    | 0.91                 | 0.9         | 90.0          | 100.0         | 5.9           |

The analysis of the obtained results allowed us to establish that the indicators of frequency of occurrence of signs of karyolysis and karyorexis in tissue cells in the area of lichen planus lesion have absolute diagnostic value: the sensitivity and specificity of tests is 100%, which excludes both false negative and false positive results (figure 1, figure 2).

An additional confirmation of the diagnosis can be the determination of the frequency of detection of perinuclear vacuoles and karyopyknosis (figure 3, figure 4). The Sensitivity of the presented tests is 90% with 100% specificity. This means that the possibility of overdiagnosis is reduced, and the probability of false negative results is eliminated. Thus, to detect lichen planus of women aged 50 and older than 60 years, we can use the frequency values for detecting diagnostically informative nuclear changes in buccal epithelial cells in the affected area, which are presented below (table 2).
Figure 3. ROC-curve of the "perinuclear vacuole" indicator for diagnostics lichen planus.

Figure 4. ROC-curve of the "karyopyknosis" indicator for diagnostics lichen planus.

Table 2. Values of the frequency of occurrence of prognostically informative nuclear abnormalities (%) in buccal epithelial cells of women over 50 years, recommended for the diagnosis of lichen planus.

| Core anomaly       | Sick people     | Healthy        |
|--------------------|-----------------|----------------|
| Karyolysis         | Less 0.9        | Than more 0.9  |
| Karyorhexis        | Than more 1.1   | Less 1.1       |
| Perinuclear vacuole| Less 7.0        | Than more 7.0  |
| Karyopyknosis      | Than more 5.9   | Less 5.9       |

4. Conclusions
Recognition of nuclear anomalies against the background of nuclear destruction makes it possible to diagnose red lichen planus in patients.

The ROC analysis of the studied signs showed that the frequency of occurrence of karyolysis and karyorexis in the cells of the affected areas of lichen planus are absolute predictors of this disease.

To confirm the diagnosis, we can recommend the determination of the frequency of occurrence of perinuclear vacuoles and karyopyknosis in cells from the affected area [6-14].

5. References
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