

# Diagnostic value of the PDD method in evaluation of vulvar lesions

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## Summary

*Purpose:* The purpose of this study was to evaluate the efficiency of photodynamic diagnostics (PDD), a method used in the diagnosis of vulvar lesions, and to determine its position and efficacy among diagnostic techniques generally used up to now.

The projected purpose of the study in cases of vulvar lesions was realised by performing a detailed comparative analysis of sensitivity, specificity and diagnostic efficacy of PDD and vulvoscopy, as compared with histological evaluation of excised lesions.

*Key words:* Photodynamic diagnostic method; Vulvoscopy; Vulvar lesions.

## Introduction

In the present study, photodynamic diagnostics (PDD) and vulvoscopy efficiency in diagnosing vulvar lesions were compared. The following parameters were evaluated: sensitivity, specificity, efficacy, and positive and negative prognostic value of both methods. A high level of consistency was observed between the photodynamic examination and the histological diagnosis, particularly important in the case of precancerous and cancerous lesions of the vulva, reaching 93%. A precise location determination of lesions with PDD may be used in the choice of appropriate treatment methods, often influencing the extension or limitation of the treatment procedure.

The incidence of vulvar cancer is considered to represent 3-5% of all malignancies of the female genital tract [1-4]. Recently, an increased incidence of this malignancy is being noted [2, 5-9]. It is related to the extended mean life expectancy in women. Vulvar cancer occurs more often in older age. It is usually appears on the vulva as a single lesion. In 25-30% of cases, it has a multi-focal nature. On the macro scale, one can differentiate exo- and endophytic forms. Despite examination availability, diagnosis of the disease and beginning treatment are delayed in an important number of cases. Almost half of the patients are in disease clinical Stage III and IV at diagnosis. Diagnostic difficulties may occur in early cancer stages developing in the vulvar epithelium, such as hypertrophic lesions, particularly in cases of multi-focal lesions. Early diagnosis is based on vulvoscopic examinations and histological analysis of tissue samples taken from vulvar lesions.

Histological examination is the basis of diagnosing a vulvar neoplastic process. Specific tissue sampling taken under colposcopic control helps to precise the diagnosis, which is then a basis for adequate treatment initiation.

Recently, the photodynamic method has been considered a procedure that aids in diagnosing neoplastic processes. It uses the property of selective, local photo-toxic action on neoplastic cells in a laser-exposed area [10-14]. The PDD method and photodynamic therapy (PDT) are relatively new procedures used in the detection and treatment of neoplastic diseases. In recent years, dynamic developments have been observed in studies related to the introduction of this method into routine clinical practice. The reasons for investigator interest in its application in the diagnosis of neoplastic processes are both the biophysical phenomenon in tissues occurring under the influence of light, resulting in a proper fluorescence in cells activated with laser light – called auto-fluorescence, and in tissues, in which an exogenous pigment has been absorbed.

Photodynamic therapy is based on the neoplastic cell destruction phenomenon sparing healthy tissues caused by physical reactions induced by an exogenous photosensitizer selectively accumulating in neoplastic tissues. Those reactions result in the appearance of active chemical compounds which destroy pathological cells.

## Materials and Methods

The study material consisted of 29 patients aged 25 to 79 years, treated at the Chair and Clinic of Obstetrics and Gynaecology of the 2nd Faculty of Medicine of Warsaw Medical University between 1998 and 2003 for existing vulvar pathologies. The indications for diagnostics were vulvar dystrophic lesions, polyps and ulcerations, including patients with vulvar pruritus without apparent macroscopic lesions.

All patients underwent vulvoscopy and PDD examination; 5-Ala (5-aminolevulinic acid hydrochloride) was used as a photosensitizer for the photo-diagnostic examination in the form of 15% cream (manufactured by Jelfa). The photo-sensitizer was administered onto the vulva six hours prior to the PDD examination. Pubic pilosity was removed before the beginning of the examination. In order to obtain fluorescence, the tissue was administered energy in the form of light coming from a 300W

xenon lamp with a wavelength of 400-420 nm. Tissue fluorescence was considered as a positive result suggesting the possibility of a neoplastic process. All procedures were performed in a location with reduced lighting in order to minimize the degradation of porphyrins.

After PDD examination, patients underwent tissue sampling from lesions in order to obtain a histological diagnosis. Tissue samples were taken from locations found suspect in vulvoscopy. The microscopic examination was estimated as non-malignant in the following pathologies: vulvitis chronica, polypi fibrosi, verucca seborrhagica, lichen sclerosus, dystrophia mixta, dystrophia atrophica and dystrophia hyperplastica. The histological result was considered as malignant in the following cases: VIN III, carcinoma planoepitheliale invasivum, carcinoma basocellulare cutis vulvae.

The evaluation of PDD and vulvoscopy efficiency in the evaluation of vulvar lesions was performed based on their comparison with histological examination results. The evaluation included their sensitivity, efficacy and specificity as well as positive and negative prognostic value.

Statistical analysis of obtained results was performed based on the following techniques:

- Student's t-test for independent assays;
- Student's t-test for dependent assays;
- Chi-square Pearson's test and Yates-modified chi-square test;
- Fisher's test.

Results with  $p < 0.05$  were considered to be statistically significant.

Analyses were performed using the STATISTICA software package, version 5.5 by StatSoft.

## Results

### *Efficiency of vulvoscopy in the diagnosis of malignant vulvar lesions.*

Table 1 presents the results of vulvoscopy and histological examinations obtained in 29 patients by focal biopsy of vulvar lesions.

Table 1. — *Comparison of vulvoscopy results with histological results.*

| Vulvoscopy<br>n = 29 | Histological examination |                |
|----------------------|--------------------------|----------------|
|                      | Malignant lesions        | Benign lesions |
| Suspect<br>14        | 10                       | 4              |
| Non-suspect<br>15    | 2                        | 13             |
| Overall              | 12                       | 17             |

$p < 0.01$ .

In 14 patients with suspect vulvoscopy, histological confirmation of a malignant process was obtained in ten cases (71.4%). In this group the diagnosis of planoepithelial carcinoma was obtained in nine cases, one patient being diagnosed with basocellular carcinoma (cutis vulvae).

In 15 patients with non-suspect vulvoscopy, consistency with histological examination was obtained in 13 cases (86.6%).

In the analyzed material, there were four cases of false positive vulvoscopy results (2 cases of lichen sclerosus and 2 cases of dystrophia atrophica), and two false negative cases of VIN III.

### *Efficiency of PDD examination in the diagnosis of malignant vulvar lesions.*

Table 2 presents results of PDD and histological examinations obtained in 29 patients by focal biopsy of vulvar lesions.

Table 2. — *Comparison of PDD results with histological results.*

| PDD<br>n = 29         | Histological examination |                |
|-----------------------|--------------------------|----------------|
|                       | Malignant lesions        | Benign lesions |
| Fluorescence<br>14    | 12                       | 2              |
| No fluorescence<br>15 | 0                        | 15             |
| Overall               | 12                       | 17             |

$p < 0.01$ .

In 14 patients in whom 15% Ala cream was used and vulvar tissue by fluorescence-induced laser light was observed, a histological confirmation of the malignant process was obtained in 12 cases (85.7%). There were nine cases of invasive planoepithelial carcinoma, one case of basocellular carcinoma cutis vulvae and two cases of VIN III in this group.

In 15 patients in whom tissue fluorescence was not observed, consistency with histological diagnosis was obtained in all 15 cases (100%).

In the analyzed material, there were two false positive results in the following cases: one case of vulvitis chronica and one case of verucca seborrhagica; there were no cases of false negative results.

Table 3. — *PDD results depending on the histological diagnosis.*

| Histological results                   | No. | Fluorescence after Ala |     |
|--|-----|------------------------|-----|
|  |     | No.                    | No. |
| Verucca seborrhagica                   | 1   | 1                      | 0   |
| Vulvitis chronica                      | 1   | 1                      | 0   |
| Polypi fibrosi                         | 2   | 0                      | 2   |
| Lichen sclerosus                       | 6   | 0                      | 6   |
| Dystrophia atrophica                   | 3   | 0                      | 3   |
| Dystrophia hyperplastica               | 1   | 0                      | 1   |
| Dystrophia mixta                       | 3   | 0                      | 3   |
| Dystrophia gr. maioris<br>VIN III      | 2   | 2                      | 0   |
| Carcinoma planoepithelial<br>invasivum | 9   | 9                      | 0   |
| Carcinoma basocellular<br>cutis vulvae | 1   | 1                      | 0   |
| Total                                  | 29  | 14                     | 15  |

Based on statistical analysis evaluating the efficiency of the photodynamic examination performed according to the study methodology in patients with vulvar lesions, the following conclusions may be formulated:

Compared to vulvoscopy, photodynamic diagnostic procedures are characterized by:

- superior sensitivity - 100% as compared to 83.0% in vulvoscopy ( $p = 0.166$ ),
- superior specificity - 88.2% as compared to 76.0% in vulvoscopy ( $p = 0.163$ ),
- superior efficacy - 93.0% as compared to 79.0% in vulvoscopy ( $p = 0.043$ ),

- superior positive prognostic value - 85.7% as compared to 71.0% in vulvoscopy ( $p = 0.171$ ),
- superior negative prognostic value - 100% as compared to 86.0% in vulvoscopy ( $p = 0.08$ )

The above results are illustrated in Figure 1.

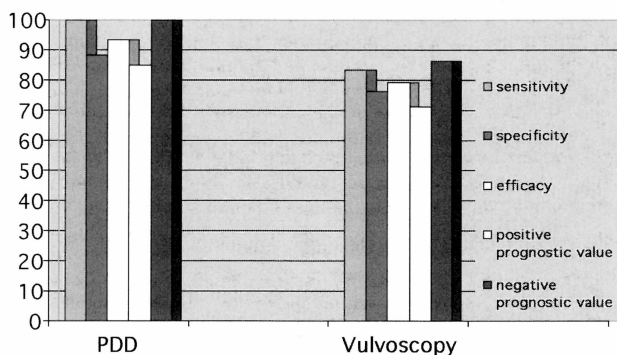


Figure 1. — Comparison of PDD and vulvoscopy examinations in terms of sensitivity, specificity, efficacy, and positive and negative prognostic value in patients with vulvar lesions.

## Discussion

The improvement of social and economic conditions has led to an extended life expectancy of the female population. The incidence of certain malignancies, including vulvar cancer, increases with age. According to the worldwide literature, the morbidity peak for vulvar cancer is observed in the seventh of decade life [2]. Other authors' reports [5-9, 19] indicate an increased occurrence of VIN and vulvar cancer in younger women. Epidemiological data and morphologic examination results suggest different vulvar carcinogenesis mechanisms in young women as compared with postmenopausal women [15-19]. Literature reports suggest, that VIN lesions as well as invasive vulvar cancer in young women are often multi-focal and that there is a possibility of co-existing intraepithelial neoplasia and invasive cancer located in the cervix and vagina [6, 7, 17-20]. In postmenopausal women, single lesions are more frequent, developing on a dystrophic background. An increased risk of transformation into invasive vulvar cancer has been found in this group [21].

Despite examination availability, the diagnosis of the disease and beginning treatment are delayed in an important number of cases. Almost half of the patients are in disease clinical Stage III and IV at diagnosis.

Malignancy diagnosis difficulties often appear in early cancer stages, when cancer develops in a vulvar hyperthrophic epithelial lesion, especially in cases of multi-focal growth.

The importance of vulvoscopy in the diagnosis and observation of vulvar lesions is generally approved and remains one of the most effective tests in the detection of vulvar precancerous lesions and vulvar cancers [5-9, 15-21].

In our material, we performed an analysis of vul-

voscopy efficiency in identifying malignant vulvar lesions based on results obtained by specific histological biopsies.

Results of studies analyzing the consistency of vulvoscopic diagnosis in young women with the final histological result, published by Adamek [5], refer to a diagnostic pertinence of 84.5%. This consistency is slightly superior to the one obtained in our material. This may result from the fact that the former study concerned a selected group of women with VIN-type lesions.

As reported by Andersson and Block [16], the consistency of vulvoscopic examination in women with diagnosed VIN-type lesions was estimated to be 66%.

Basta [17] obtained an elevated correlation of results (reaching 88.5%) of vulvoscopic examination in women with diagnosed VIN.

Many authors [5, 16, 17, 20] emphasize the high utility of vulvoscopic examination in the diagnosis of vulvar precancerous lesions and malignancies.

Despite numerous reports on the subject and the availability of the diagnosed organ, the diagnosis of early stages of the disease must be considered unsatisfactory.

Considering the still unsatisfactory clinical composition of patients starting treatment (excessive numbers of advanced stage disease), it was pertinent to include in our study diagnostic procedures based on the PDD method and to evaluate their utility in the diagnosis of vulvar lesions.

The application of the PDD method in the diagnostic process of vulvar lesions constitutes the subject of only a few reports in the Polish and worldwide literature. None of these reports includes a comprehensive workup of the method in relation to the nature of the cancer and its clinical stage. There is also univocal information missing regarding the choice of the photo-sensitizer, its concentration (between 10 and 20%, according to various authors) and the application method, and also the use of optimal laser light sources.

Results of studies on local application of a 10% 5-aminolevulinic acid in the diagnostics of vulvar diseases, performed in 107 patients with VIN I-III type lesions or cancer, published by Kindah *et al.* [22], revealed sensitivity, specificity, positive and negative prognostic values to be respectively 92.9%, 90.2%, 91.2% and 92.0%. Those results were consistent with our studies.

Walt and Hornung [23] and Korell [24] also obtained results similar to ours, with the difference that the latter used a greater than 20% concentration of 5-aminolevulinic acid.

The photodynamic diagnostics of vulvar lesions, similarly to vulvoscopic examination, bear a certain error. This error may be the result of many factors. Obtaining false results (both false-positive and false-negative results) depends on the nature of the chosen photo-sensitizer, on the time between its application and exposure to laser light as well as on the choice of a proper wavelength of the laser light.

Despite those difficulties, our results, confirmed by the literature data [22-24], seem to suggest an important

utility of the diagnostic photodynamic method in the diagnosis of vulvar malignancies; however, one should not forget that the histological examination remains the basis for final diagnosis.

The value of the photodynamic examination is undoubtedly unquestionable in the detection of vulvar cancer in early stages through tissue fluorescence observation and its localisation, which in turn helps the following specific biopsy, importantly improving the accuracy of pre-therapeutic diagnoses. It should also be mentioned that the direct evaluation of fluorescence (in the case of both mucosa and pubic skin, in contrast to vulvoscopy examination) provides information on the multi-focal character of lesions and on their range, which in turn may constitute a basis for further prognostics.

Knowledge of the actual location of malignant vulvar lesions allows for the use of less mutilating treatment methods.

## Conclusions

1. An important consistency of the photodynamic examination with histological diagnosis was observed, particularly high in cases of vulvar precancerous lesions and malignancies, reaching 93%.

2. A superior accuracy of the PDD method was observed compared to vulvoscopy examinations - 79%.

3. The possibility of performing a one-time specific biopsy of lesions found during the photodynamic examination helps improve the accuracy of histological diagnoses.

4. Fluorescence observation and the possibility of evaluating its intensity during the photodynamic examination may constitute the basis for determining the range or multi-focal character of lesions.

5. Precise localisation of lesions using photodynamic diagnostics may be used in the choice of appropriate treatment methods, often influencing the extension or limitation of the treatment procedure.

6. No adverse events were observed when performing local photodynamic diagnostic procedures.

7. Encouraging accurate studies allows us to popularize photodynamic diagnostics in gynecological practice in order to improve diagnostic accuracy, for example in the so-called cumulative analysis of the results of various methods.

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