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# PHOTODYNAMIC (FLUORESCENCE) DIAGNOSTICS OF SKIN LESIONS

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## INTRODUCTION

The growing incidence of cutaneous malignancies each year [1] necessitates the development of new and more effective methods for the diagnosis of cancerous lesions, while assuring better treatment results and improving patient satisfaction [2]. Unlike the formerly used, only systemically - applicable haematoporphyrin derivates (HpD), the recently developed topical photosensitizers 5-aminolevulinic acid (ALA) or its methyl ester (methyl aminolevulinate - MAL) induce photosensitizing porphyrins [3]. The targeted photosensitization of skin cancer, particularly superficial and extensive lesions including superficial basal cell carcinoma and Bowen's disease, by ALA or MAL induced porphyrins leads to a selective red fluorescence which can be demonstrated by Wood's lamp or other appropriate light source [4]. This technique may be useful to define lesion margins better and/or to detect multifocal recurrences earlier. Performed early, fluorescence diagnosis has been shown to be highly efficient for superficial non-melanoma skin cancer despite the low level of invasiveness.

Porphyrin-enriched tumour tissue irradiation with fluorescence excitation system leads to emission of pink-red fluorescence. This principle is used as a diagnostic procedure and is called photodynamic diagnosis (PDD), also known as fluorescence diagnosis (FD)[5].

In PDD, porphyrin fluorescence is detected under irradiation with different lights (under blue or near - UV excitation in range 300-450 nm) [6]: a Wood light (370-405 nm) [7], xenon lamp (375-400 nm) [8], mercury lamp (400 nm, 405±15 nm) [9,10], a krypton ion laser with a 405 nm wavelength [9], 370 nm [11], 410 nm [11, 12], a Blu-U light system that uses visible blue light [9], blue light at 380-440 nm [13], the violet

excitation wavelength at 405 nm is used as it matches the PpIX fluorescence excitation peak (the Soret band) well [12, 14, 15], light diodes (401 nm) and others. We used light source composed of seven light diodes in order to determine which wavelength suits best for diagnosing the tumour with particular histological structure. Our light source produced light in range of 378 to 426 nm with seven different waves.

In patients with advanced or small recurrent skin cancer PDD can improve the efficacy of the treatment [16]. These lesions may represent atherapeutic and diagnostic challenge because of special subtypes, location, previous therapy or accompanying diseases. Fluorescence can help in effective detecting and delineating of neoplastic areas. Recently, the use of photodynamic diagnosis and therapy has been proposed for the management of cancer [17-20]. Despite the easy accessibility mechanism to adequately screening and detecting premalignant changes and early lesions in the skin, fluorescence diagnosis is being attempted as diagnosis modality with the potential to bridge the gap between clinical examination and invasive biopsies [11]. In order to further enhance the tumor demarcation, exogenous sensitising agents can be administered. Several groups are carrying out research to develop fluorescence diagnosis methods for early detection of premalignant lesions, most of them using as photosensitizer ALA or its methyl ester – induced protoporphyrin IX (PpIX). Aminolevulinic acid has been shown to be the drug with most experimental and clinical use [5, 17]. No generalized photosensitivity has been reported following topical ALA/MAL application, and ALA-induced PpIX appears to be almost completely cleared from the body within 24 h of its induction [14]. Topical ALA/MAL application does not provide prolonged generalized photosensitivity. The mostly used agent (in

past) is hematoporphyrin derivative (Photofrin), originally developed for photodynamic therapy (PDT) by intravenous administration. In therapeutic doses it exhibits an unwanted side - effect of transient skin sensitisation, which lasts for at least 1-2 weeks. Topically active agents are preferable for PDD and PDT, and most experience to date has been with ALA or its methyl ester [6].

In our study we compared PDD for tumours with different histological structure made using seven different wavelength light sources and both ALA and MAL topical sensitizing agents.

## THE AIM OF THE STUDY

The aim of this study was to investigate the diagnostic value and methodological features of photodynamic (fluorescence) diagnostics in skin lesions.

## OBJECTIVES

1. To examine the sensitivity, specificity, positive predictive value and negative predictive value of photodynamic diagnostics of non-melanoma skin cancer.
2. To compare the effectiveness of different photosensitizer precursors (5-aminolevulinic acid and methyl-aminolevulinate) at inducing fluorescence of skin tumours.
3. To investigate the possibilities of photodynamic diagnostics in skin lesions using light sources with different wavelength and to determine the optimal wavelength of light to diagnose tumours of different histological types.

4. To evaluate similarities and differences of fluorescence in malignant and premalignant skin lesions.
5. To investigate the ability of photodynamic diagnostics in determining exact margins of skin tumours before and during the treatment

## SCIENTIFIC NOVELTY

In absence of scientifico-clinical studies exploring the value of fluorescence diagnostics in malignant skin lesions, fluorescence diagnostics in such lesions was performed. The sensitivity and specificity of PDD were estimated. Light sources with different wavelength were compared during the study. Their applicability for PDD in general and distribution according to different histological types of skin lesions were analyzed. There are no data from studies comparing the possibilities of PDD using light sources with different wavelength published in neither local nor available global literature.

## MATERIALS AND METHODS

Photodynamic diagnostics measurements were performed at the laboratory of Laser and Photodynamic Treatment (Institute of Oncology, Vilnius University) 2006 – 2009 using data of 136 patients with 379 malignant, premalignant and benign skin lesions, for detection of the foci of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). The study “Photodynamic diagnostics of skin and mucosal lesions” approved by Lithuanian Bioethics Committee (2006-09-08 No. 38. and 2006-12-22 No.

62). These tests were carried out with informed patient consent. Two different precursors of photosensitizer protoporphyrin IX have been used – the topical application of 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL).

PDD was carried within 2 to 4 hours after topical ALA - 20% cream of 5-aminolevulinc acid (MEDAC GmbH Hamburg, Germany) on Exsipiale basement application or within 3 hours after topical MAL - Metvix - 16% cream of methyl aminolevulinate (Photocure ASA**,** Oslo, Norway) application. The cream was applied topically with a 1 cm margins surrounding the lesion, an occlusive dressing covered the cream. The sensitizer PpIX is synthesized by the haem cycle in the cells to highly elevated levels due to the amounts of ALA or MAL applied [21]. The lesions were not specifically prepared before performing fluorescent diagnostics. Before administering photodynamic therapy we usually remove scales and crusts by curettage or laser destruction. For the diagnostic procedure the lesions were not particularly prepared in order to assess and differentiate the glowing of the lesions as if they were seen the first time.

As fluorescence excitation system we used the light system based on blue light emitting diodes that allows easy switching from conventional white-light mode to an ALA/MAL - induced violet-blue light (378-426 nm) mode (Table 1).

**Table 1.** Characteristics of light diodes composing light source

| Emitted light peak (nm) | 378 | 389 | 392 | 401 | 405 | 408 | 426 |
|---|---|---|---|---|---|---|---|
| Emission angle (º) | ± 5 | ± 15 | ± 10 | ± 15 | ± 12 | ± 12 | ± 15 |
| Emission intensity (mW) | 1 | 2 | 2 | 2 | 10 | 3 | 3-6 |

The instrument was designed to provide multi-spectral (seven band) light. Its functional feature is capability to switch between white light imaging and fluorescence imaging with multiple emission wavelength bands, using all of them together or separately. Diagnostic illumination usually lasted for 5 to 30 seconds. Two or three doctors separately assessed the fluorescence that was seen. Results were summarised and the average was calculated. In the beginning of the study the spectroscopic analysis was performed for ten lesions. That afforded to compose and to use a visual scale reasonably. Finally, a digital camera was used for taking pictures of the fluorescenting area. Different wavelengths were delivered in ascending order. After the blue light inspection, biopsy samples from tumour foci were taken. The evaluated fluorescence data were compared with cytological and/or histopathological tissue investigation.

## RESULTS AND DISCUSSION

Visible tumour nodules were found to be fluorescent, whereas no fluorescence was observed in normal skin and mucosa. In the blue light mode, there is background blue fluorescence in normal tissue and red fluorescence in malignant areas (Figure 1).

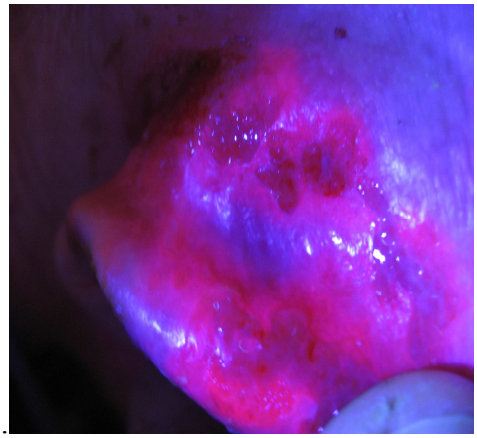
**A.**  **B.** 

**Figure 1.** Photodynamic diagnostics of squamous cell carcinoma on the helix of the ear. **A)** Before fluorescence diagnosis **B)** During illumination of tissues, red-pink fluorescence of malignant areas (after ALA application)

Intensity and even other changes of fluorescence was evaluated and compared with pathological findings. Red or red-pink fluorescence was observed in 221 malignant epithelial tumours; 192 of them fluorescent sharp, 29 - not so intensive, 7 malignant tumours - had no fluorescence (Table 2,3).

The most intensive red fluorescence was detected in thin superficial malignant lesions. In 9% tumour foci were identified with the blue light in an area that initially appeared normal when examined with the conventional light. All tumour foci were carcinomas or premalignant lesions confirmed histologically (by biopsy).

**Table 2.** ALA - induced fluorescence intensity according tumours morphology

| Morphology | Fluorescence | | | Total |
|---|---|---|---|---|
| | Sharp | Less intensive | No | |
| Basal cell carcinoma (BCC) | 98 | 11 | 5 | 114 |
| Squamous cell carcinoma (SCC) | 12 | 1 | - | 13 |
| Premalignant lesion | 17 | 12 | 1 | 30 |
| Benign lesion | - | 19 | 21 | 40 |
| **Total** | **127** | **43** | **27** | **197** |

p<0,001

**Table 3.** MAL - induced fluorescence intensity according tumours morphology

| Morphology | Fluorescence | | | Total |
|---|---|---|---|---|
| | Sharp | Less intensive | No | |
| Basal cell carcinoma (BCC) | 75 | 17 | 1 | 93 |
| Squamous cell carcinoma (SCC) | 7 | - | 1 | 8 |
| Premalignant lesion | 7 | 15 | 1 | 23 |
| Benign lesion | 1 | 10 | 47 | 58 |
| **Total** | **90** | **42** | **50** | **182** |

p<0,001

Attention should be paid to lesions showing only moderate fluorescence in the skin, as this might already indicate the onset of carcinoma in situ [8]. The additional information we received from this method may be of great significance. Fluorescence of premalignant and benign lesions was different from malignant - not so red, bluer and less intensive.

No or in a few cases very slight fluorescence was observed in benign lesions. From 98 benign lesions, very slight fluorescence was detected in a few haemangiomas and

paratracheal papillomas, two foci of Darier diseases, one fragment of herpes zoster and some superficial open wounds with very intensive capillarity. Papillomas, seborrhoeic keratoses and scars had no fluorescence.

Patients have not noted any subjective symptoms such as pain, itching, burning sensation or other during diagnostic procedure. These observations confirm a good efficacy and tolerance of PDD in the cohort of cancer patients.

Recent technological advances in light sources, high-sensitivity imaging detectors, and high-performance spectrographs, together with advances in digital imaging/processing, are enabling a wide variety of medical applications [10]. In our study we paid more attention to light sources used for fluorescence diagnosis, because in many PDD studies mainly photosensitizers are analysed and compared, paying less attention to light sources. It is known that porphyrins show five strong absorption peaks. The absorption spectrum of them exhibits a maximum in the so-called Soret band ranging from 360 to 400 nm. Maximum of absorbance is around at 405 nm. This maximum is followed by additional 4 peaks with decreasing intensity between 500 and 635 nm (Q-Bands). For PDD, light around 405 nm is used [15,22]. For this reason one of the objectives of our study was to analyse the fluorescence produced separately by different light sources having wavelength with near-maximum or maximum absorbance. The fluorescence of skin and mucosa tumours with different histological structure was examined.

Performing PDD with different wavelength light sources it was found that for assessing malignant skin cancer the optimal wavelength is 401 nm. During illumination with light having such wavelength the brightest fluorescence of malignancies (bright raspberry colour) is seen. Usage of that particular wavelength delineates the border

between lesion and healthy tissue best. Intact skin do not fluorescent and remain coloured blue. Light having wavelength of 389 nm serves better for detecting premalignant lesions (Table 4).

**Table 4.** Fluorescence intensity according morphology and fluorescence excitation (++++ sharp; +++ intensive; ++ less intensive; + minimal)

| | **Fluorescence** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Fluorescence excitation, nm** / **Morphology** | 378 | 389 | 392 | 401 | 405 | 408 | 426 |
| Basal cell carcinoma (BCC) | - | ++ | + | +++ | ++ | + | - |
| Squamous cell carcinoma (SCC) | - | ++ | + | ++++ | ++ | + | - |
| Condyloma acuminata | - | +++ | - | ++ | + | - | - |
| Actinic keratosis (ACC) | - | ++ | - | ++ | + | - | - |
| Seborrheic keratoses | - | - | - | - | - | - | - |

After analysing different wavelength light sources used for performing PDD it was found that the optimal wavelength is 401 nm. It is interesting to notice that authors who studied photosensitizers refer to 405 nm as maximum absorbance peak [15, 22], whereas the brightest fluorescence of skin and mucosa malignancies was seen under light with wavelength of 401 nm in our study. Light having wavelength of 405 nm produced fluorescence too, but not as bright as of 401 nm. It is possible that in organism photosensitizers have peak absorbance at 401 nm in skin malignancies, but it is an object of more detailed investigations.

We had interesting experience – green fluorescence was seen when infiltrative carcinoma was illuminated with light having wavelength of 426 nm. While illuminating

with 426 nm light not intense dark green to grey fluorescence was seen in case of eight patients. In areas producing fluorescence of such colour focus of infiltrative carcinoma under the healthy skin was confirmed instead of superficial lesion. As reviewed by Yang et al. green fluorescence had been seen, but in other tissues: connective tissue rich in collagen and elastin fibers, such as bone and dura, appeared green in the composite fluorescence image, as would be expected from the known fluorescence spectra of these molecules [10].

In review of similar works there were noticed that results are very similar and the best fluorescence was observed in superficial basal cell carcinoma and squamous cell carcinoma while benign lesions had no fluorescence [12,14,26]. The fluorescence contrast is of great importance for the reliability of PDD technique when demarcating tumour tissue from normal skin. There was exclusive possibility to compare the use of two photosensitizers for PDD in this study.

After the early studies using ALA, the majority of clinical studies have involved the topical application of MAL to skin lesions [9], without their comparison. In our study, after examination of 379 skin lesions, in 30% of cases the delineation of neoplastic lesions excited by ALA, was slightly weaker than using MAL. The same efficacy of PDD has been observed for ALA and MAL in this study (Table 5).

**Table 5.** The diagnostic value of photodynamic diagnostics

| **Morphology** | Basal cell carcinoma | | Squamous cell carcinoma | | Premalignant lesion | | Carcinomas | |
|---|---|---|---|---|---|---|---|---|
| **PDD** | ALA | MAL | ALA | MAL | ALA | MAL | ALA | MAL |
| **Sensitivity** | 89,5 | 95,7 | 92,3 | 87,5 | 70,0 | 87,0 | 92,9 | 95,1 |
| **Specificity** | 81,9 | 91,0 | 97,3 | 97,1 | 90,4 | 95,0 | 85,7 | 84,0 |
| **Positive predictive value** | 87,2 | 90,8 | 70,6 | 58,3 | 56,8 | 71,4 | 88,1 | 88,1 |
| **Negative predictive value** | 85,0 | 95,3 | 99,4 | 99,4 | 94,4 | 98,1 | 85,7 | 93,2 |
| κ (Kappa) value | 0,718 | 0,868 | 0,784 | 0,683 | 0,551 | 0,75 | 0,626 | 0,798 |

Sensitivity of 94.3%, specificity of 81.5% as well as positive and negative predictive values of 87.7% and 90.8%, respectively, were obtained of photodynamic diagnostics of malignant skin lesions.

We investigated the usefulness of ALA/MAL-induced porphyrin fluorescence in preoperative demarcation of ill-defined clinical tumour margins and as a control before and after PDT. There was a strong correlation between clinical extension and fluorescence pattern of the tumours. In addition, all fluorescent areas were proved to be neoplastic by histopathologic examination. The observations in this group of patients suggest that red fluorescence may correlate with the precise of minimal (millimetre) residual malignant skin and mucosal tissue, the same was found by Yang et al. [10] studying brain tumours. Margins of tumours were clearly outlined under fluorescent vision, giving a helpful contribution to diagnosis and therapy even in clinically non-

visible tumours. Hence, the fluorescence could be used to guide surgical resection or PDT and promote better tumour tissue removal in silent areas. The use of PDD allowed delineation of clinically ill-defined tumors and detection of tumor relapses or new tumors that were not clinically detectable.

In vivo fluorescence can provide new tools for clinical oncology: screening and diagnosis of early-stage malignancy, defining tumour extent, and optimising localized treatment of solid tumours [10].

The isolation of porphyrins and the subsequent discovery of their tumour-localizing properties led to the development of modern photo detection [9, 24] – PDD. Advanced or recurrent cancer tissue may be difficult to differentiate from abnormalities induced by previous surgical procedures, such as granulomas and scars. In addition to functioning as a novel therapeutic tool, photodynamic sensitisation of skin cancer cells is increasingly used for photodynamic diagnosis. The fluorescence of induced porphyrins is effective in detecting and delineating neoplastic areas [5,25]; it helps to recognize the appearance of small tumour foci.

PDD is a simple diagnostic method, without any doubt this technique has found a practical role in everyday clinical practice. Despite some previously expressed thoughts from several authors [23] that it will not be a clinically useful method it is clear evidence that sometimes it is impossible to manage without PDD (e.g., determine radicality of treatment after surgical operation and especially after PDT), also large cutaneous malignancies can present a diagnostic challenge. Fluorescence imaging is an attractive diagnostic technique for skin and mucosal tumors demarcation with potential to move to clinical use.

## CONCLUSIONS

1. Topical photodynamic diagnostic method can be fairly accurate in detecting skin cancer. This method was found to have a sensitivity of 94.3%, a specificity of 81.5% as well as positive and negative predictive values of 87.7% and 90.8% respectively.
2. Fluorescence of similar intensity was found after comparing ability of different applications (5-aminolevulinic acid and methyl-aminolevulinate) to induce fluorescence in skin lesions. In 30% of cases the delineation of neoplastic lesions excited by 5-aminolaevulinic acid was slightly weaker than using methyl aminolevulinate application
3. In order to achieve complete visualization of skin lesions after the application of a tumour selective photosensitizer the most appropriate wavelength of light-emitting diode for photodynamic diagnostics is 401 nm in malignancies and 389 nm in premalignant lesions
4. Premalignant skin lesions are fluorescenting as well as malignancies when using photodynamic diagnostics but less intensively and with bluish red colour.
5. Photodynamic diagnostic method helps to delineate margins of malignant skin lesions with precision of several millimetres.

- Fluorescence diagnostics is well tolerated, quite simple, valuable and informative diagnostic method in detecting early primary malignant epithelial skin tumours as well as possible recurrences after treatment and in delineation of obscure margins of malignancies.

## PRACTICAL RECOMMENDATIONS

- Photodynamic diagnostics is recommended in following cases:

1. Before, during, and after all photodynamic therapy procedures in order to evaluate thoroughness of treatment.
2. In all ambiguous cases when skin cancer is suspected but the most suitable site for biopsy for histological examination is unclear.
3. In order to delineate margins of malignant skin lesion before treatment (surgical, laser or cryodestructive)

- It is recommended to use the single and most effective wavelength of light source to induce the most intensive fluorescence. It is 401 nm in skin malignancies and 389 nm in premalignant skin lesions.

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**SANTRAUKA**

Sergamumas odos vėžiu pastaruoju metu sparčiai didėja – tai dažniausi piktybiniai navikai baltosios rasės populiacijoje visame pasaulyje. Literatūros duomenimis, odos vėžys sudaro 12-14 % visų piktybinių navikų. Literatūroje gausu nuorodų apie pasaulinę odos vėžio epidemiją [1].

Ankstyvoji odos vėžio diagnostika, taip pat mažos apimties recidyvų diagnostika ir gydymas tampa vienomis iš aktualiausių onkodermatologijos problemų. Nors iš pirmo žvilgsnio gali pasirodyti, kad atpažinti odos vėžį nėra sudėtinga, nes tai labiausiai matomas žmogaus organas, tačiau taip nėra. Dažnai būna ypač sunku diagnozuoti labai ankstyvą odos vėžį, atsirandantį ikivėžinių pažeidimų fone, taip pat nustatyti mažus recidyvus po gydymo susidariusiuose randuose. Onkodermatologijoje naudojami įvairūs diagnostiniai metodai: dermoskopija, ultragarsinis tyrimas. Tačiau histopatologinis tyrimas išlieka pats svarbiausias nustatant klinikinę diagnozę. Bet ir šiuo metodu ne visuomet galima nustatyti tikslias naviko ribas, kai pažeisti arba labai dideli plotai, arba sritys, kur svarbu išsaugoti kiekvieną sveikos odos milimetrą. Todėl sukurti nauji, mažiau invaziniai diagnostiniai metodai, pasižymintys ypatingu tikslumu ir leidžiantys nesukelti pacientui skausmo juos taikant [11].

Fotodinaminė diagnostika (FDD) – metodas, naudojamas ankstyvojoje ir pirminėje navikų ir recidyvų diagnostikoje, t.p. gydymo metu, nustatant tikslias naviko ribas, po gydymo tikrinant gydymo radikalumą [5]. Tai labai perspektyvus vizualizacijos metodas onkologijoje, kurio metodikos dar neištobulintos ir visuotinai nepatvirtintos. Nėra galutinai (tiksliai) įvertintas odos navikų FDD metodo specifiškumas ir jautrumas. Todėl svarbu ištirti odos navikų fotodinaminės (fluorescencinės) diagnostikos

diagnostinę vertę (jautrumą, specifiškumą, teigiamą prognozinę vertę ir neigiamą prognozinę vertę) ir metodo ypatumus.

## DARBO TIKSLAS

Ištirti odos navikų fotodinaminės (fluorescencinės) diagnostikos metodo diagnostinę vertę ir ypatumus.

## DARBO UŽDAVINIAI

1. Ištirti odos piktybinių epitelinių darinių fotodinaminės diagnostikos metodo jautrumą, specifiškumą, teigiamą prognozinę vertę ir neigiamą prognozinę vertę.
2. Palyginti skirtingų fotopreparatų (5-aminolevulino rūgšties ir metilo aminolevulinato) sąlygotą fluorescenciją odos navikuose.
3. Ištirti odos fotodinaminės diagnostikos metodo galimybes, naudojant skirtingo bangos ilgio šviesos šaltinius ir nustatyti šviesos bangos ilgį, optimalų diagnozuoti skirtingų histologinių tipų odos navikus.
4. Įvertinti ikivėžinių ir piktybinių odos darinių fluorescencijos tapatumus ar skirtumus.
5. Ištirti odos navikų ribų nustatymo fotodinaminės diagnostikos metodu galimybes prieš gydymą ir gydymo metu.

## MOKSLINIS NAUJUMAS

Trūkstant mokslinių-klinikinių darbų apie fluorescencinės (fotodinaminės) diagnostikos metodo reikšmę nustatant odos piktybinius navikus, atliktas tokių navikų fluorescencinės diagnostikos tyrimas, įvertinant FDD metodo jautrumą ir specifiškumą. Šio tyrimo metu buvo palyginti įvairių bangos ilgių šviesos šaltiniai, jų tinkamumas FDD apskritai bei jų tinkamumas diagnozuojant įvairių histologinių tipų odos navikus. Įvairių šviesos bangos ilgių panaudojimo FDD palyginamojo pobūdžio darbų nėra nei lietuviškoje, nei prieinamoje pasaulinėje literatūroje.

## TYRIMO MEDŽIAGA, METODAI IR NAUDOTA APARATŪRA

2006 – 2009 m. Vilniaus universiteto Onkologijos instituto Lazerinės ir fotodinaminės terapijos laboratorijoje fotodinaminės diagnostikos metodu ištirti 136 pacientai. Diagnozuota plokščialąstelinės, bazoląstelinės karcinomos bei ikivėžiniai dariniai ir nustatytos tikslios jų ribos.

Tyrime dalyvavo abiejų lyčių asmenys, vyresni nei 18 metų (vyrai – 35,3%, moterys – 64,7%), kuriems kliniškai buvo įtartas ar morfologiškai nustatytas odos vėžys. Tiriamųjų amžius svyravo nuo 27 iki 91 metų. Iš viso fotodinaminės diagnostikos metodu išanalizuoti 379 dariniai.

Fotodinaminė diagnostika buvo atliekama prieš aplikacinę fotodinaminę terapiją, jos metu, tuoj po jos ar prieš kitokį gydymą (chirurginį, lazerdestrukcinį) tikslioms riboms nustatyti, išplitimui įvertinti. FDD metodu nustačius gerybinį darinį ir diagnozę patvirtinus morfologiškai nebuvo taikoma aplikacinė FDT.

Taikant aplikacinės fluorescencinės diagnostikos metodą naudoti fotopreparatai: 5-aminolevulino rūgštis (ALA) ir/ar metilo aminolevulinatas (MAL).

Po 2-4 val nuvalę kremą, tiriamo ploto paviršiaus audinius 2-5 sekundes apšviesdavome skirtingų bangos ilgių šviesa ir vertinome audinių švytėjimą (fluorescenciją), bei nustatėme bangos ilgį šviesos, kuria apšvietus audinius sužadinama intensyviausia fluorescencija. Tam naudojome unikalų aparatą, skleidžiantį 7 skirtingų bangos ilgių šviesą (bangos ilgio - λ diapazonas kinta nuo 370 nm iki 420 nm) (1 lent.).

**1 lentelė.** Šviesos šaltinio charakteristikos

| Spinduliuo-jamos šviesos smailė (nm) | 378 | 389 | 392 | 401 | 405 | 408 | 426 |
|---|---|---|---|---|---|---|---|
| Spinduliuotės kampas (laipsniais) | ± 5 | ± 15 | ± 10 | ± 15 | ± 12 | ± 12 | ± 15 |
| Spinduliuotės intensyvumas (mW) | 1 | 2 | 2 | 2 | 10 | 3 | 3-6 |

Nustatyta fluorescencija kiekvieną kartą buvo vertinama pagal vaizdinę skalę atskirai dviejų ar trijų gydytojų chirurgų, rezultatai susumuojami ir pateikiamas vidurkis. Darbo pradžioje buvo atlikta dešimties darinių FDD ir spektroskopinė analizė, atliekant sklindančios šviesos fizikinius matavimus. Tai įgalino sudaryti ir pagrįstai naudoti matomą vaizdinę skalę. Fluorescencija fotografuota skaitmeniniu fotoaparatu ir duomenys saugomi kompiuterinėje laikmenoje.

FDD procedūrų metu iš visų švytinčių sričių, o įtariant piktybinį procesą tiek iš fluorescuojančių, tiek iš nešvytinčių židinių buvo imama medžiaga morfologiniam tyrimui. Pagal gautus histologinio ar citologinio tyrimo atsakymus buvo vertinama tiriamo audinio morfologijos ir švytėjimo koreliacija.

## REZULTATAI

Ištyrę 379 odos darinius, nustatėme, kad piktybinių navikų audinys fluorescuoja ryškiai raudonai avietine spalva ir švytintis plotas melsvai violetiniame sveikų audinių fone išsiskiria aiškiomis ribomis. Iš ištirtų 229 odos epitelinių piktybinių darinių, 192 fluorescavo intensyviai, 29 – stebėtas neintensyvus švytėjimas, 7 visai nefluorescavo (2,3 lent.).

**2 lentelė.** ALA-FDD fluorescencijos intensyvumo priklausomybė nuo darinių morfologijos

| | **Fluorescencija** | | | **Iš viso** |
|---|---|---|---|---|
| | **Intensyvi** | **Neintensyvi** | **Nėra** | |
| **Bazoląstelinė karcinoma** | 98 | 11 | 5 | 114 |
| **Plokščialąstelinė karcinoma** | 12 | 1 | 0 | 13 |
| **Ikivėžinis darinys** | 17 | 12 | 1 | 30 |
| **Gerybinis darinys** | 0 | 19 | 21 | 40 |
| **Iš viso** | 127 | 43 | 27 | 197 |

$p<0,001$

**3 lentelė.** MAL sąlygotos fluorescencijos intensyvumo priklausomybė nuo darinių morfologijos

| | **Fluorescencija** | | | **Iš viso** |
|---|---|---|---|---|
| | **Intensyvi** | **Neintensyvi** | **Nėra** | |
| **Bazoląstelinė karcinoma** | 75 | 17 | 1 | 93 |
| **Plokščialąstelinė karcinoma** | 7 | 0 | 1 | 8 |
| **Ikivėžinis darinys** | 7 | 15 | 1 | 23 |
| **Gerybinis darinys** | 1 | 10 | 47 | 58 |
| **Iš viso** | 90 | 42 | 50 | 182 |

$p<0,001$

Bazoląstelinės karcinomos – dažniausi odos navikai, diagnozuoti šiuo metodu. Iš viso ištyrėme 207 bazaląstelines karcinomas, iš jų – 17 navikų buvo diagnozuoti tik pagal fluorescenciją. Tirtose srityse nebuvo matoma pažeidimų, būdingų klinikiniam bazoląstelinės karcinomos vaizdui. Atlikus FDD minėti židiniai buvo patvirtinti histologiniu tyrimu kaip bazoląstelinė karcinoma. FDD metodu nustatėme tikslias išplitimo ribas prieš gydymą (patvirtinta morfologiniais tyrimais), tai būtina siekiant gydymo radikalumo. Taip pat 1 židinį iš 5 karcinomų *in situ* aptikome tik pasitelkdami FDD metodu.

Odos darinių švytėjimo skirstinys pagal fluorescencijos intensyvumą, sukeltą skirtingų bangos ilgių šviesos, pateikiamas 4 lentelėje. Ištyrus 379 navikus, nustatyta, kad intensyviausiai FDD metu švyti plokščialąstelinė karcinoma (++++) apšviesta 401nm šviesa. Ši šviesa taip pat sužadina labai intensyvią (+++) bazoląstelinės karcinomos fluorescenciją. Smailiagalės karpos **(***Condyloma acuminata*) ryškiau švytėjo

(+++) apšvietus šviesa, kurios bangos ilgis 389 nm. Aktininių keratozių fluorescencija buvo vienodai neintensyvi (++) apšvietus 389 nm bei 401 nm šviesa. Fotodinaminės diagnostikos metu tirtos seborėjinės keratozės nešvytėjo.

**4 lentelė.** Židinio pobūdžio ir fluorescencijos priklausomybė

| | **Fluorescencija** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Šviesos bangos ilgis, nm** / **Morfologija** | 378 | 389 | 392 | 401 | 405 | 408 | 426 |
| Bazoląstelinė karcinoma (BLK) | - | ++ | + | +++ | ++ | + | - |
| Plokščialąstelinė karcinoma (PLK) | - | ++ | + | ++++ | ++ | + | - |
| Smailiagalė karpa | - | +++ | - | ++ | + | - | - |
| Aktininė keratozė (AK) | - | ++ | - | ++ | + | - | - |
| Seborėjinė keratozė | - | - | - | - | - | - | - |

FDD metodu ištyrus 379 odos darinius apskaičiuotos pagrindinės šio vizualizacijos metodo charakteristikos (5 lent.)

**5 lentelė.** FDD metodo charakteristikos

| **Darinys** | Bazoląstelinė karcinoma | | Plokščialąstelinė karcinoma | | Ikivėžinis pažeidimas | | Visos karcinomos | |
|---|---|---|---|---|---|---|---|---|
| **Fotopreparatas** | ALA | MAL | ALA | MAL | ALA | MAL | ALA | MAL |
| **Jautrumas** | 89,5 | 95,7 | 92,3 | 87,5 | 70,0 | 87,0 | 92,9 | 95,1 |
| **Specifiškumas** | 81,9 | 91,0 | 97,3 | 97,1 | 90,4 | 95,0 | 85,7 | 84,0 |
| **Teigiama prognozinė vertė** | 87,2 | 90,8 | 70,6 | 58,3 | 56,8 | 71,4 | 88,1 | 88,1 |
| **Neigiama prognozinė vertė** | 85,0 | 95,3 | 99,4 | 99,4 | 94,4 | 98,1 | 85,7 | 93,2 |
| κ (Kappa) koficientas | 0,718 | 0,868 | 0,784 | 0,683 | 0,551 | 0,75 | 0,626 | 0,798 |

Nustatėme bendruosius odos piktybinių epitelinių navikų fotodinaminės diagnostikos (naudojant fotopreparatus ALA ir MAL) kokybę charakterizuojančių rodiklių rezultatus: jautrumas – 94,3%, specifiškumas – 81,5%, teigiama prognozinė vertė – 87,7%, neigiama prognozinė vertė –90,8%.

## IŠVADOS

1. Aplikacinės fotodinaminės diagnostikos metodu galima gana tiksliai nustatyti odos vėžį. Šio tyrimo jautrumas – 94,3%, specifiškumas – 81,5%, teigiama prognozinė vertė – 87,7%, neigiama prognozinė vertė – 90,8%.
2. Palyginus skirtingų fotopreparatų (5-aminolevulino rūgšties ir metilo aminolevulinato) odos navikuose sąlygotą fluorescenciją nustatyta, kad abiem atvejais fluorescencija vienodo intensyvumo. 30% atvejų tikslesnės ribos tarp naviko ir sveiko audinio nustatytos naudojant metilo aminolevulinatą.
3. Tinkamiausias odos piktybinių navikų fotodinaminėje diagnostikoje diodinis šviesos šaltinis, kurio bangos ilgis yra 401 nm, o ikivėžinių darinių atveju – 389 nm.
4. Ikivėžiniai odos dariniai fotodinaminės diagnostikos metu fluorescuoja kaip ir piktybiniai, tačiau mažiau intensyviai ir melsvai raudona spalva.
5. Fotodinaminė diagnostika padeda nustatyti piktybinių odos navikų ribas milimetrų tikslumu.

- Fotodinaminė diagnostika yra lengvai ligonių toleruojamas, palyginti paprastas ir informatyvus diagnostinis metodas tiek nustatant tiek pirminius, ankstyvuosius piktybinius epitelinius odos navikus ir galimus jų recidyvus po gydymo, tiek tikslinant neaiškias piktybinio proceso išplitimo ribas.

## PRAKTINĖS REKOMENDACIJOS

- Fotodinaminę diagnostiką rekomenduojama atlikti:
  1) prieš visas fotodinaminės terapijos procedūras, jų metu ir po fotodinaminio gydymo – radikalumui pasiekti ir įvertinti.
  2) esant neaiškiems klinikiniams atvejams, kai įtariamas odos vėžys, bet kyla abejonių, iš kurios vietos imti biopsinę medžiagą histologiniam ištyrimui;
  3) odos piktybinio naviko riboms patikslinti prieš gydymą (chirurginį, lazerdestrukcinį, kriodestrukcinį).

- Intensyviausiai fluorescencijai sužadinti rekomenduojama naudoti vieną veiksmingiausio bangos ilgio šviesą: odos piktybinių navikų atveju – 401nm, o ikivėžinių pažeidimų atveju – 389nm.

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