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# LIGHT-INDUCED FLUORESCENCE SPECTROSCOPY AND OPTICAL COHERENCE TOMOGRAPHY OF BASAL CELL CARCINOMA

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Many up-to-date optical techniques have been developed and applied recently in clinical practice for obtaining qualitatively and quantitatively new data from the investigated lesions. Due to their high sensitivity in detection of small changes, these techniques are widely used for detection of early changes in biological tissues. Light-induced fluorescence spectroscopy (LIFS) is one of the most promising techniques for early detection of cutaneous neoplasia. Increasing number of recent publications have suggested that optical coherence tomography (OCT) also has potential for non-invasive diagnosis of skin cancer. This recent work is a part of clinical trial procedure for introduction of LIFS technique into the common medical practice in National Oncological Medical Center in Bulgaria for diagnosis of non-melanoma skin cancer. We focus our attention here on basal cell carcinoma lesions and their specific features revealed by LIFS and OCT analysis. In this paper we prove the efficiency of using the combined LIFS-OCT method in skin lesions studies by integrating the complimentary qualities of each particular technique. For LIFS measurements several excitation sources, each emitting at 365, 385 and 405 nm maxima are applied. An associated microspectrometer detects *in vivo* the fluorescence signals from human skin. The main spectral features of the lesions and normal skin are discussed and their possible origins are indicated. OCT images are used to evaluate the lesion thickness, structure and severity stage, when possible. The obtained results could be used to develop a more complete picture of optical properties of these widely spread skin disorders. At the same time, our studies show that the combined LIFS-OCT method could be introduced in clinical algorithms for early tumor detection and differentiation between normal/benign/malignant skin lesions.

*Keywords*: Cutaneous fluorescence; OCT BCC images; endogenous porphyrins; skin cancer.

## 1. Introduction

Cutaneous cancer is the second cause of newly developed tumors every year, for both males and females, covering about 10% of all new cancer sites. Amongst them, basal cell carcinoma is the most wide-spread type of skin neoplasia, appearing in about 70% of all new cases.[1] In combination with the fact that the number of new cancer patients

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grows from year to year, the interest in medical community for development and introduction of non-invasive, fast and reliable procedures for detection and evaluation of this kind of tumors has increased rapidly during the last decade. In such conditions, initial clinical trials for evaluation of diagnostic applicability of light-induced fluorescence spectroscopy for non-melanoma tumors are currently underway.[2]

Biological tissues contain chromophores that absorb light, as well as fluorophores that absorb and re-emit (fluoresce) light. Tissues are heterogeneous by character and promote strong light scattering. The tissue optical properties such as absorption, fluorescence, reflectance and scattering can be used to characterize the tissue and to identify tissue abnormalities using non-invasive and real-time optical techniques. Fluorescence spectroscopy is applied to the analysis of many different types of samples, ranging from individual biochemical species, to whole organs *in vivo*. Light-induced fluorescence spectroscopy (LIFS) is one of these non-invasive methods that can identify diseases and increase the knowledge in medical diagnosis.[3,4] Investigators have already applied this technique for the detection of endogenous fluorophores occurring in the tissue[5−7] as well as for exogenous fluorescent dyes used for a better differentiation between normal and abnormal skin sites.[8,9] This spectroscopic approach has been investigated for the diagnosis of almost every type of cancer and neoplastic changes in human body.[10] Fluorescence technique with or without exogenous fluorescent markers added also finds many other applications — for monitoring of pathogenic bacteria photoinactivation processes,[11] for dosimetry of photodynamic therapy procedures,[3,10,12] and for drug uptake analysis.[4,12] Autofluorescence spectroscopy is used for diagnosis and follow-up of dermatological diseases, such as erythrasma and acne.[13] The investigation possibilities of this technique include applications for evaluation of vitiligo,[14] erythema,[5] and skin photoaging.[4] LIFS is also used for skin cancer detection and lesion type determination.[3,4,10,12]

Optical coherence tomography (OCT) provides high-resolution, depth-resolved images of scattering tissues. With micron-scale resolution and millimeter depth of imaging, OCT is very appropriate for examination of superficial tissues and pathologies. The image is a result of detected backscattered signal, which originates from index of refraction mismatches in the tissue under investigation. OCT is applied to *in vivo* detection of microvascular changes during photodynamic therapy,[15] image-guided surgery analysis,[16] monitoring of wound healing,[17] laser treatment results evaluation,[18] and mostly imaging of different skin lesions, including cancer detection.[18−20]

OCT instrumentations are commercially available, providing two-dimensional images of high resolution in lateral and axial directions of morphological microstructures of the skin. Compared to high-frequency sonography, OCT images are more detailed in structural information and contrast.[18] The limitation, however, is the low penetration depth of the light into the skin. Due to the strong scattering of skin tissue, imaging is possible to a depth of about 1.5–2 mm. However, for many cases this is enough to identify alterations in the structure of the dermal layers down to the upper dermis. One important aspect reported by different groups is that OCT technique has low specificity and could not distinguish different non-melanoma tumor sub-types. Also variability in OCT image characteristics is much smaller in intra-patient than inter-patient situations,[19−21] which reduces its applicability for clinical usage as a single diagnostic technique.

Given the fact that basal cell carcinoma has several different sub-types, it is difficult to be correctly diagnosed even by an expert dermatologist. Light-induced fluorescence spectroscopy (LIFS) has very high sensitivity for detection and evaluation of different cutaneous neoplasia types and stages of growth, but could not give information about the structure and geometry of the pathology. OCT, on the other hand, allows very good observation of the morphology with low sensitivity to the sub-type of pathology observed. Common usage of both techniques gives all aspects needed for clinical diagnosis — high sensitivity for early stage lesions and their type and precise image of the pathology with possibility for structural feature evaluation, such as depth, thickness, and dimensions.

## 2. Materials and Methods

The present investigation is a part of a clinical trial for introduction of spectroscopic diagnostic system for skin cancer detection in the common practice of dermatological department of National Oncological Center, Sofia.

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### 2.1. *Clinical diagnosis*

In the present study 23 patients of the National Oncological Medical Center with basal cell carcinoma diagnosis are included. Patients are classified by Fitzpatrick classification (Wolff *et al.*, 1977, cited in Ref. 22) with skin phototype II and phototype III, the most common cutaneous types for the region. The average age of patients is 67 and the range is from 43 to 88 years. Four patients have more than one tumor detected. All lesions observed are systematically diagnosed by standard and fluorescence techniques, and in total 28 lesions are evaluated and presented in this study.

Initially, the lesions were classified visually by an experienced dermatologist (E.P.) and dermatoscopically. Each lesion was evaluated using ABCD scoring criteria as follows: Asymmetry (A), Border (B), Color (C) and Dermoscopic structures (D). All lesions have been histologically examined by standard methods. The histological examination was used as a "gold" standard for determination of lesion type, and final analysis of spectroscopic techniques feasibility was made.

### 2.2. *Light-induced fluorescence spectroscopy*

After visual and dermatoscopic classification, as a second step fluorescence signals from lesion and surrounding normal skin were detected using light-emitting diodes as excitation sources, with different emission wavelengths, namely 365, 385, and 405 nm (5 mW output power, $\theta = 20°$, FWHM = 15 nm). Optical fiber bundle (QR-600-7-UV-125F, Ocean Optics Inc., Dunedin, FL, USA) was used to deliver the light from LEDs (six surrounding illumination fibers) and to collect the fluorescence signal (one read fiber).

A constant distance of two millimeters between the end tip of the optical fibers and the skin surface was applied, using a mechanical stand to avoid any influence of displacement from the normal position on the intensity level. All spectra were obtained at normal incidence — at the 90° angle between optical fibers end tip and skin surface.

The spectra were recorded and stored using a fiber-optic microspectrometer (USB4000, Ocean Optics Inc., Dunedin, FL, USA). A personal computer was used to control the system and to store and display the data using the specialized microspectrometer software OOI Base ("Ocean Optics", Inc., Dunedin, FL, USA).

Spectroscopic measurements of normal skin and lesion areas were carried out after five minutes of rest for each patient at room temperature (23 to 25°C). Several spectra were measured from each suspicious area and averaged to reduce the influence of inhomogeneity of the lesions. Three to five spectra were recorded and averaged from every lesion, depending on its size, and three spectra from surrounding normal skin. These averaged spectra from the healthy skin area were used like an indicator of the spectral changes in the pathological areas. The spectra were smoothed using a Savitzky–Golay algorithm in order to reduce the instrumental noise of the spectrometric system.

### 2.3. *OCT measurements*

Optical coherence tomography measurements have been performed using a Thorlabs OCP930SR Spectral Radar OCT imaging system. This system combines a broadband light source with a high-speed spectrometer to perform Fourier domain detection of the OCT interference fringe signals.

Both normal skin and lesion have been measured with a 930-nm light source, optical power 2 mW. Images have been acquired at eight frames per second, image width being set to a maximum of 6 mm and image size to 512 rows. The spectral radar system has a 100-nm spectral bandwidth, which yields a typical imaging depth of ∼1.6 mm, lateral resolution of 20 $\mu$m and an axial resolution of 6.2 $\mu$m. The instrument is equipped with non-contact and contact tips, both of them being used for measuring the lesions. An integrated CCD camera has been used for sample monitoring.

## 3. Results and Discussion

Organized by the National Oncological Medical Center in Sofia, this project aimed to introduce fluorescence spectroscopy as a method of early cutaneous tumor diagnosis, with special attention being paid to combining LIFS and OCT techniques for the detection of non-melanoma cutaneous malignancies. Basal cell carcinoma is one of the most interesting malignancies, due to the fact that about 70% of all new skin cancer sites are BCC lesions.

Figure 1 shows OCT images of normal skin surface and two BCC lesions of one patient. According

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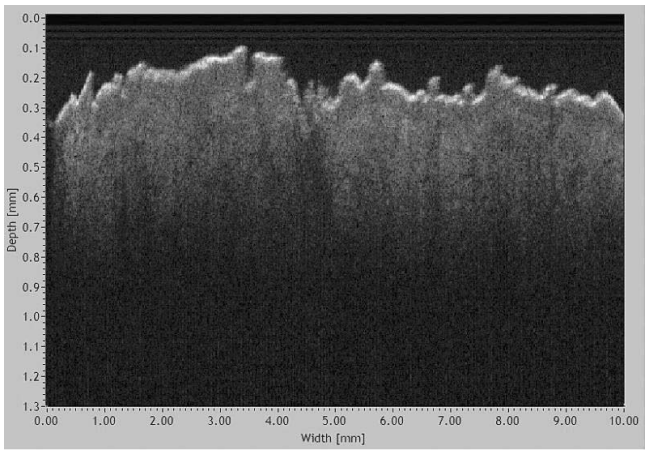
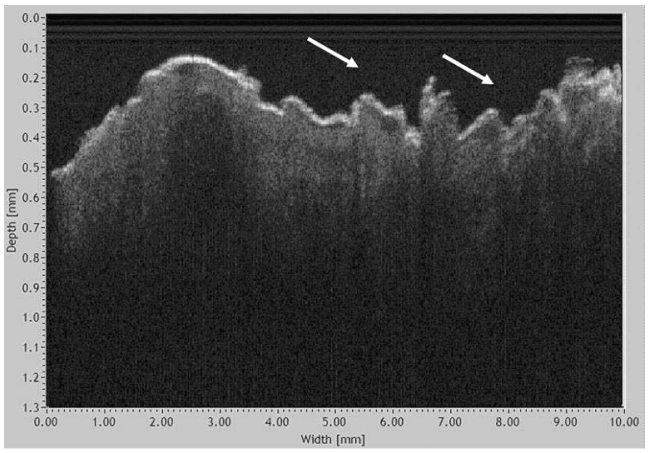
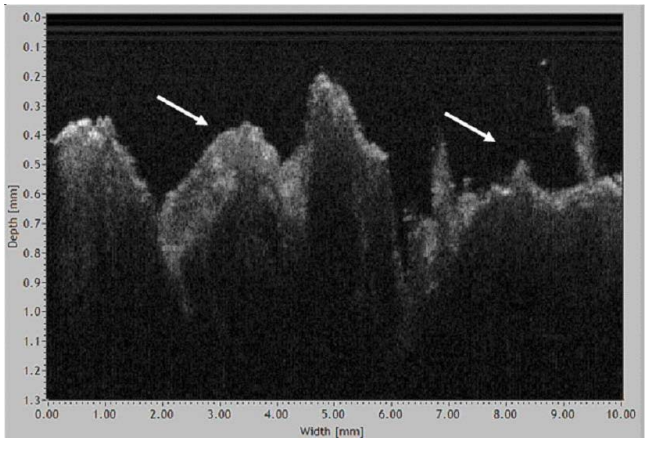



(a)




(b)




(c)

Fig. 1. OCT images of (a) normal skin, (b) eight-month-old BCC lesion, and (c) two-year-old BCC lesion in one patient.

to information from the patient, one of the lesions appeared about two years before the observation; the second one appeared about eight months before the light-induced fluorescence and OCT measurements were carried out. It was a good opportunity to compare features, which appear on different stages of the BCC lesion growth, without complications of inter-patient differences, which could influence our results. Intra-patient differences could be taken as negligible, due to the fact that both pathologies were near anatomic places. On the OCT images strong difference is clearly observed between tumor surfaces for the initial and advanced stage lesions. In the first case, we observed some disarrangement of the epidermal layer and loss of layered structure of epidermis–derma typical for the healthy skin. However, for the advanced stage of BCC pathology this pattern is much more pronounced and we observe total loss of epidermal structures in the image detected, with deep disruptions on the lesion surface.

Compared to non-lesional skin, a loss of normal skin architecture and disarrangement of the epidermis and upper dermis were observed in all OCT images of malignant lesions. All BCC sites investigated demonstrated excellent correlation of tissue thickness, up to 1 mm in depth, estimated by optical coherence tomography and routine histopathologic tests. This depth correlation was consistent across all malignancies observed. However, OCT images do not allow separating with high diagnostic accuracy the sub-types of BCC lesions observed. OCT images allow delineating tumor borders with very good repeatability and visualization of the edges, as well as to the depth of the lesions for superficial BCC cases. Our observations correlate with the conclusions of other investigators about OCT applicability in BCC diagnosis.[19,20]

The accuracy of OCT measurements reported by other groups for skin cancer detection and evaluation is about 80%.[23,24] Nevertheless, in comparison with ultrasound cutaneous imaging, OCT is capable of showing very small cystic structures more distinctly; in terms of assessing the margins of the tumor, ultrasound is discussed as possible better choice.[25] When OCT is applied for detection of neoplastic changes in different mucosal layers, diagnostic accuracy reported is about 78% for esophagus, 92% for bladder, and 88% for colon.[26]

Imagining depth of acquired OCT images is lower in the case of skin lesions due to the structural changes which appear in tumoral sites. The imaging depth for normal skin is up to 700 $\mu$m, as for the lesion is $\sim$200 $\mu$m.

In Fig. 2 are presented histopathological results for the initial and advance stages of BCC lesions

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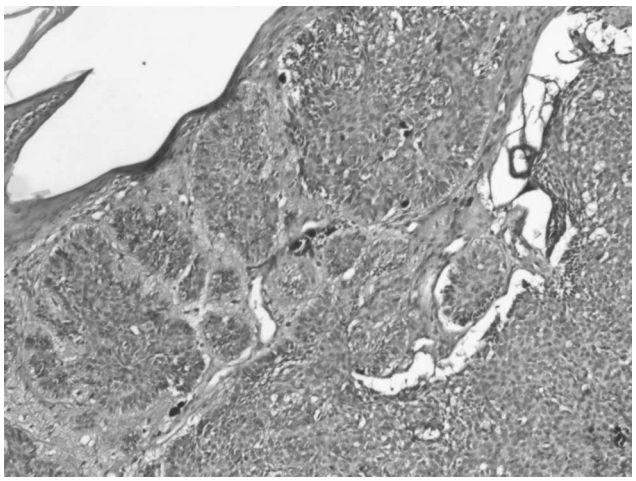
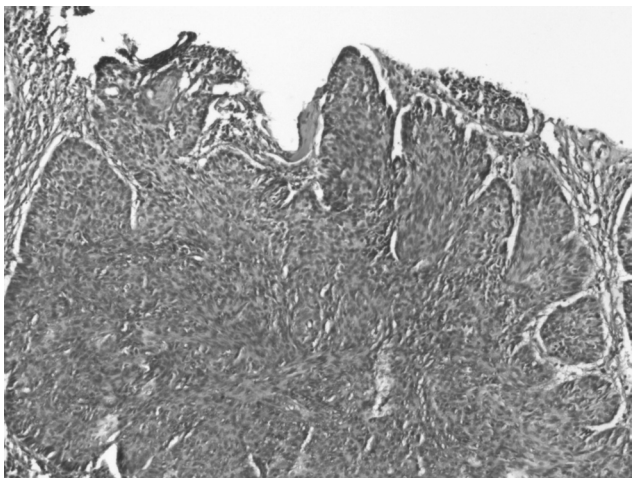
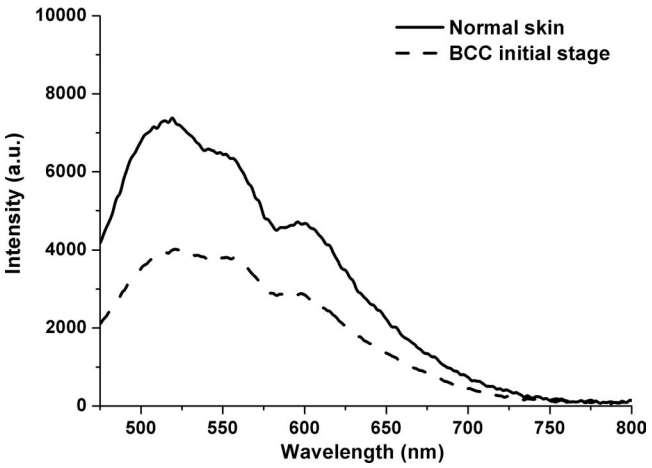


(a)

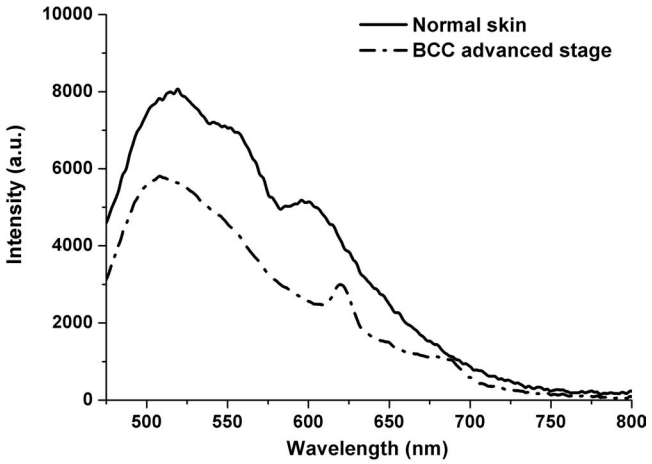


(b)

Fig. 2. Histological images of superficial (a) initial stage BCC lesion, and (b) advanced stage BCC lesion in one patient.




(a)




(b)

Fig. 3. LIF spectra comparison of normal skin with (a) eight-months-old BCC lesion, and (b) two-years-old BCC lesion, using excitation at 405 nm in one patient.

observed in the patient. Topographical correlation between the histologically confirmed lesions and OCT images was observed.

In Fig. 3 light-induced fluorescence spectra are presented, that have been obtained from the same patient as the OCT images presented on Fig. 1 are from. Normal skin fluorescence spectra from the surrounding of the lesion investigated are given to compare with the initial- and advanced-stage basal cell carcinoma lesions.

Fluorescent maxima in the region 630–700 nm are clearly observed in the case of advanced stage of BCC tumor. Such signal has been observed in three other cases, where the BCC has been detected in advanced stage of growth (1.5 or more years old). This signal could be related to the endogenous porphyrins, which appear in the advanced stages of tumor development.[3,9]

Other chromophores related to the formation of autofluorescence signals observed are mainly structural proteins, their cross-links, co-enzymes and lipids.[4] The resultant spectrum detected *in vivo* is a superposition of these compounds with different contribution of manifestation for every excitation wavelength. Fluorescent compounds are collagen type I — at 400–405 nm; its cross-links — at 460–490 nm; elastin — with maxima at 400–420, 460 nm; elastin cross-links — about 500 nm maximum of fluorescence; NADH — at 440–470 nm; keratin — at 430–460 nm, and around 500–520 nm, flavins.[4,5,7,26] Influence of melanin and hemoglobin pigments is observed in the received fluorescence spectra related

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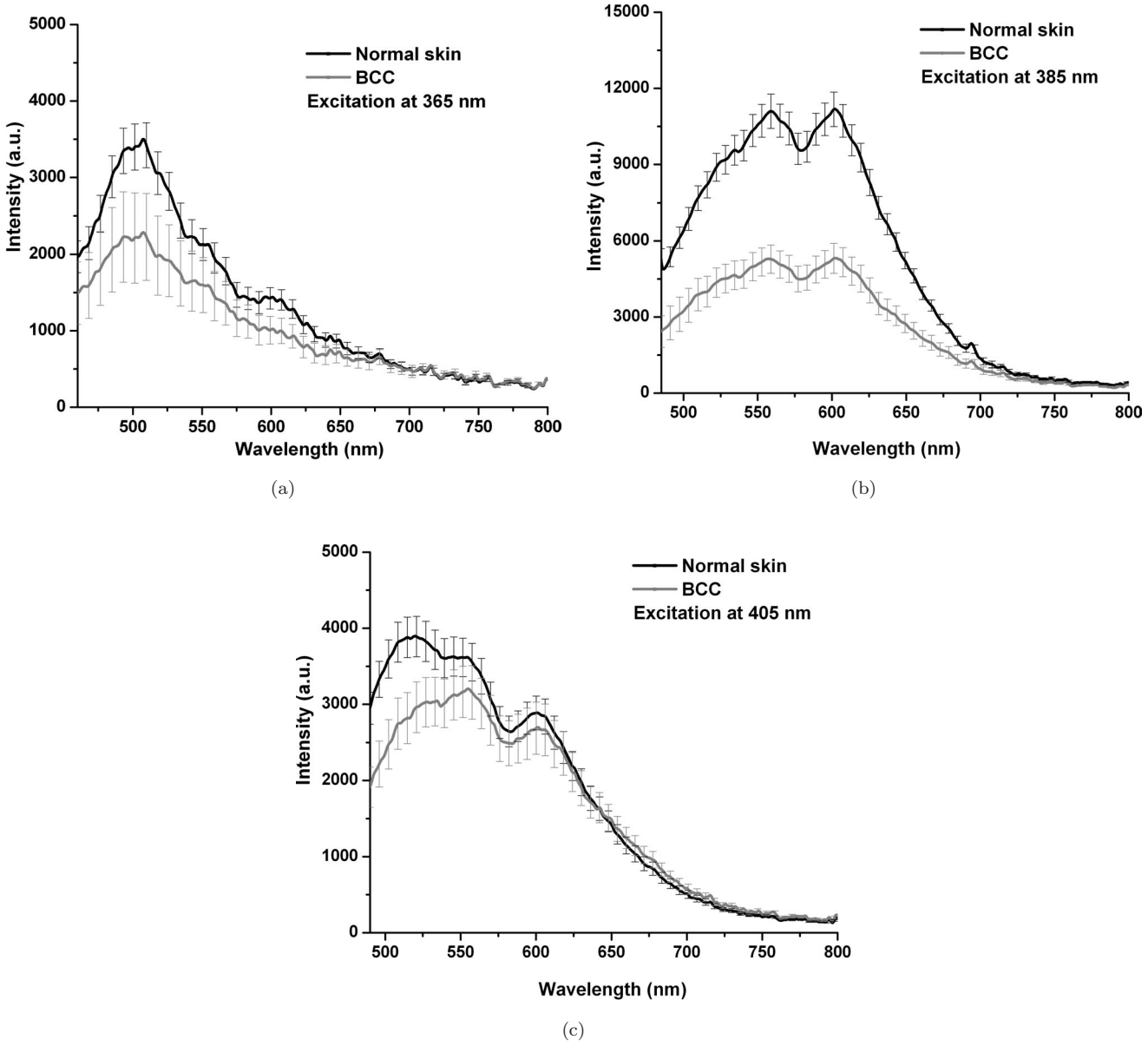


Fig. 4. Fluorescence spectra of normal and cancerous skin averaged for all patients using excitation at (a) 365 nm, (b) 385 nm, and (c) 405 nm. Spectra are presented with their standard deviation after averaging for all lesions detected.

to bigger decrease of the short-wavelength intensity versus long-wavelength intensity, as well as appearance of minima at 420, 543 and 575 nm, respectively.

In Fig. 4, a comparison of normal skin and BCC fluorescence spectra for the three excitation sources is presented. Spectra are averaged for all patients investigated.

The fluorescence intensity of normal skin is higher for all cases observed, and the oxyhemoglobin influence is more pronounced (re-absorption of the fluorescence signal at 543 and 575 nm). This effect is observed in all comparisons between skin phototypes and it is related to different levels of screening absorption effect of the melanin in epidermal layer. Besides lower fluorescence intensity in the case of tumor, different fluorescence signals of the tumor were observed, in comparison with fluorescence signal of the normal skin in the spectral region around 380–460 nm; the observation was clear for the cases when shorter wavelength excitation was applied.

OCT detects coherently backscattered light, whereas LIFS detects fluorescence emission of a variety of endogenous fluorophores. Complimentary mechanisms of contrast for OCT and LIF, when used in combination, could provide more sensitive

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detection of disease than either modality alone. These two types of information may also facilitate broader signal interpretation and increase in specificity.[26] LIFS intensity is highly dependent upon the probe-sample separation and OCT can provide geometrical information needed with high accuracy. In the opposite, LIFS has the potential to clarify inconclusive OCT scans. For example, Kuranov *et al.*[28] used OCT and LIFS to image neoplasms in the cervix and found that these two modalities, when combined, produced fewer false-positive results than either modality alone.

We also expected potential improvement in detection and diagnostic efficiency for cutaneous neoplasia when OCT and LIFS are applied together. OCT provides information about sub-surface structures that can aid interpretation of LIFS spectra. Quantitative measures of tissue layer thickness and probe-tissue separation can be used for better evaluation of LIFS results. At last, according to existing reports, combination of two techniques increase diagnostic accuracy for diseased tissue detection. The obtained results could be used for development of a more complete picture of optical and morphological properties of these widely spread skin disorders. This approach could be introduced in clinical algorithms for early tumor detection and differentiation between normal/benign/dysplastic/malignant skin lesions.

## 4. Conclusions

All clinical applications of optical techniques *in vivo* are based on extracting information from the optical absorption, fluorescence and scattering properties of tissues by non-invasive measurement of the fluorescence and/or diffusely reflected light. These properties are related to the function or structure of the tissue. The fluorescence spectroscopy is extremely sensitive to small changes in the human skin and to the pathology types observed, but does not give information about the thickness and morphological distribution of the lesion. OCT, on the other hand, allows imaging of the lesion, evaluation of its position, thickness and depth from the surface — which is very useful for the decision about next treatment procedures — but does not give us significant information about the lesion type itself.

In this investigation we demonstrated the potential of combined application of LIFS and OCT for differential diagnosis of the most common malignant pathology — basal cell carcinoma. The combined LIFS-OCT method offered real-time data of the fluorophore compounds found in the investigated skin and visual information about the structural changes.

By fluorescence technique we could distinguish the sub-type of the pathology and even the stage of its growth. Some of the origins of the spectral features in fluorescence spectra obtained from investigated lesions were also discussed. These results could be used for better comprehension of the skin optical properties and provide wide range of possibilities related to early diagnosis and differentiation of cutaneous diseases. A good correlation between histological analysis of the skin and repeatability of the features of the fluorescence signals from patient to patient with one-type lesion was seen. Although the number of reported cases does not permit us to create general diagnostic algorithms, the obtained results can give useful information about the investigated lesions. Clinical trial is currently under implementation and with broadening of the database that includes fluorescence spectra and images of major skin benign and malignant pathologies, we expect to develop an objective tool for detection and evaluation of skin-lesion type, based on its spectral properties.

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## References

1. S. Danon, Z. Valerianova, T. Ivanova, *Cancer Incidence in Bulgaria 2004*, volume XV, Bulgarian National Cancer Registry, Publisher "AVIS-24" Ltd. (2007).
2. E. Borisova, E. Nikolova, P. Troyanova, L. Avramov, "Autofluorescence and diffuse reflectance spectroscopy of pigment disorders in human skin," *JOAM* **10**, 717–722 (2008).
3. S. Svanberg, "Environmental and medical applications of photonic interactions," *Physica Scripta* **T110**, 39–50 (2004).
4. L. Bachmann, D. Zezell, A. da Costa Ribeiro, L. Gomes, A. Ito, "Fluorescence spectroscopy of biological tissues — A review," *Appl. Spectr. Rev.* **41**, 575–590 (2006).

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5. Y. Sinichkin, S. Utz, A. Mavliutov, H. Pilipenko, "*In vivo* fluorescence spectroscopy of the human skin: Experiments and models," *J. Biomed. Opt.* **3**, 201–211 (1998).
6. R. Na, I. Stender, L. Ma, H. Wulf, "Autofluorescence spectrum of skin: Component bands and body site variations," *Skin Res. Tech.* **6**, 112–117 (2000).
7. N. Kollias, G. Zonios, G. Stamatas, "Fluorescence spectroscopy of skin," *Vibrational Spectroscopy* **28**, 17–23 (2002).
8. V. Mantareva, D. Petrova, L. Avramov, I. Angelov, E. Borisova, M. Peeva, D. Woehrle, "Long wavelength absorbing cationic Zn(II)-phthalocyanines as fluorescent contrast agents for B16 pigmented melanoma," *J. Porphyr. Phthalocyan.* **9**, 47–53 (2005).
9. S. Andersson-Engels, J. Johansson, U. Stenram, K. Svanberg, S. Svanberg, "Malignant tumor and atherosclerotic plaque diagnosis using laser-induced fluorescence," *IEEE J. Quantum Elect.* **26**, 2207–2217 (1990).
10. T. Vo-Dinh, B. Cullum, "Fluorescence spectroscopy for biomedical diagnostics," Chap. 28 in *Biomedical Photonics Handbook*, T. Vo-Dinh, Ed., CRC Press (2003).
11. V. Mantareva, V. Kussovski, I. Angelov, E. Borisova, L. Avramov, D. Woehrle, "Photodynamic activity of water-soluble phthalocyanine zinc(II) complexes against pathogenic microorganisms," *Bioorg. Med. Chem.* **15**, 4829–4835 (2007).
12. J. Moan, L. W. Ma, V. Iani, "On the pharmacokinetics on topically applied 5-aminolevulinic acid and two of its esters," *Int. J. Cancer* **92**, 139–143 (2001).
13. H. Ahn, S. Kim, Y. Kye, "Fluorescence digital photography of acne using a light-emitting diode illuminator," *Skin Res. Tech.* **12**, 289–291 (2006).
14. E. Borisova, L. Avramov, "Laser system for optical biopsy and *in vivo* study of the human skin," *Proc. SPIE* **4397**, 405–409 (2001).
15. H. Li, B. Standish, A. Mariampillai, N. Munce, Y. Mao, S. Chiu, N. Marcon, B. Wilson, A. Vitkin, V. Yang, "Feasibility of interstitial doppler optical coherence tomography for *in vivo* detection of microvascular changes during photodynamic therapy," *Las. Surg. Med.* **38**, 754–761 (2006).
16. S. Boppart, W. Luo, D. Marks, K. Singletary, "Optical coherence tomography: Feasibility for basic research and image-guided surgery of breast cancer," *Breast Cancer Res. Treat.* **84**, 85–97 (2004).
17. W. Jung, B. Kao, K. Kelly, L. Liaw, J. Nelson, Z. Chen, "Optical coherence tomography for *in vitro* monitoring of wound healing after laser irradiation," *IEEE J. Select. Topics Quant. Elect.* **9**, 222–226 (2003).
18. R. Steiner, K. Kunzi-Rapp, K. Scharffetter-Kochanek, "Optical coherence tomography: Clinical applications in dermatology," *Med. Las. Appl.* **18**, 249–259 (2003).
19. T. Jørgensen, A. Tycho, M. Mogensen, P. Bjerring, G. Jemec, "Machine-learning classification of non-melanoma skin cancers from image features obtained by optical coherence tomography," *Skin Res. Tech.* **14**, 364–369 (2008).
20. M. Mogensen, T. Joergensen, B. Nurnbe, H. Morsy, J. Thomsen, L. Thrane, G. Jemec, "Assessment of optical coherence tomography imaging in the diagnosis of non-melanoma skin cancer and benign lesions versus normal skin: Observer-blinded evaluation by dermatologists and pathologists," *Dermatologic Surgery*, Published Online: 8 Apr 2009, doi: 10.1111/j.1524-4725.2009.01164.x.
21. V. Korde, G. Bonnema, W. Xu, C. Krishnamurthy, J. Ranger-Moore, K. Saboda, L. Slayton, S. Salasche, J. Warneke, D. Alberts, J. Barton, "Using optical coherence tomography to evaluate skin sun damage and precancer," *Las. Surg. Med.* **39**, 687–695 (2007).
22. H. Moseley, *Non-Ionizing Radiation: Microwaves, Ultraviolet and Laser Radiation*, J. W. Arrowsmith Ltd., Bristol, UK (1988).
23. N. Gladkova, N. Shakhova, B. Shakhov, "Optic coherent tomography: A new high-resolution technology of visualization of tissue structures. Communication II. Optical images of benign and malignant entities," *Vestn. Rentgenol. Radiol.* Mar–Apr (2), 44–54 (2004).
24. H. Hong, J. Sun, W. Cai, "Anatomical and molecular imaging of skin cancer," *Clin. Cosmetic Invest. Dermatology* **1**, 1–17 (2008).
25. H. Buchwald, A. Muller, J. Kampmeier, "Optical coherence tomography versus ultrasound biomicroscopy of conjunctival and eyelid lesions," *Klin. Monatsbl. Augenheilkd.* **220**, 822–829 (2003).
26. J. K. Barton, A. R. Tumlinson, U. Utzinger, "Combined endoscopic optical coherence tomography and laser induced fluorescence," in *Optical Coherence Tomography — Technology and Applications*, W. Drexler, J. Fujimoto, Eds., Springer (2008).
27. L. Wang, H. Wu, *Biomedical Optics: Principles and Imaging*, Wiley-Interscience (2007).
28. R. Kuranov, V. Sapozhnikova, H. Shakhova, V. Gelikonov, E. Zagainova, S. Petrova. "Combined application of optical methods to increase the information content of optical coherent tomography in diagnostics of neoplastic processes," *Quantum Electronics* **32**, 993–998 (2002).