

# Photodynamic therapy of malignant and benign tumours in Lithuania

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**Background.** Photodynamic therapy (PDT) involves using tumour localizing photosensitizer, followed by activation of it by light of a specific wavelength. The goal of this work was to investigate and to enlarge the possibilities of PDT in clinical radical and palliative treatment of cancer patients.

**Materials and methods.** The total of 848 patients, with both 1435 malignant and 446 precancerous tumours underwent PDT in the Institute of Oncology of Vilnius University. The morphological verification was provided in all the cases prior to the treatment. Six different lasers and one light-diode system were applied for PDT. Hematoporphyrin derivatives were used for ordinary PDT, while 5-aminolevulinic acid was applied for topical ALA-mediated PDT.

**Results.** As the result of PDT treatment, 91% of basal cell carcinomas, 75% of squamous cell carcinomas and 63% of other malignancies showed a complete response. The immediate result of PDT depended on the thickness of the malignant tumour treated. If the thickness of the tumour was narrower than 4 mm, the single PDT course was sufficient for the complete tumour regression. The exception was malignant melanoma. It required a special PDT method, the long-term multistage low power photosensitized melanoma laser lighting, gradually increasing the power of the light. Such treatment significantly prolongs the median survival of patients with recurrent and metastatical melanoma.

**Conclusions.** PDT is effective in primary and recurrent lesions as well as in primary untreated tumours and the ones for which radiotherapy or chemotherapy was provided. PDT induced photo biological changes depend on the tumour histology type.

**Key words:** photodynamic therapy, solid tumours, hematoporphyrin derivative, 5-aminolevulinic acid, lasers

## INTRODUCTION

Photodynamic therapy (PDT) involves using tumour localizing photoactive drug (photosensitizer), followed by activation of the photosensitizer by light of a specific wavelength. During PDT, a photosensitizing compound, after being introduced to target cells, is activated by a specific wavelength of light (typically visible) in order to produce cytotoxic species: strong oxidizers, namely, free radicals for “type I reaction” and singlet oxygen for “type II reaction” (1). The singlet oxygen causes direct cell killing, vascular shutdown, and host-mediated damage through the release of inflammatory and immune mediators (2). The reaction of the cytotoxic species with subcellular organelles and macromolecules (proteins, DNA etc.) lead to apoptosis and/or necrosis of the cells hosting the photosensitizer. Compared to other traditional anticancer therapies, PDT does not involve generalized destruction of healthy cells. In particular cases it can be used as a less invasive alternative to surgery (3).

The original use of photosensitizing chemicals for the therapy of various diseases dates back to ancient Egypt, India and Greece (4). The ability of visible light to damage or destroy living tissue in the presence of a photosensitizer was first clearly observed by O. Raab. In 1904, von Tappeiner described the fluorescence in protozoa after the application of aniline dyes (5). He introduced the notion of “photodynamic action” (6). In 1905, A. Jesionek (Munich) effectively used eosin and visible light in treating human skin cancer. In 1942, H. Auler and G. Banzer were the first to observe that HP was selectively retained in primary as well as in metastatic tumours (7). In 1948, F. Figge et al (Baltimore) showed that porphyrins and metalloporphyrins have a selective affinity for neoplastic, embryonic and regenerating tissues in rodents (8). The current era of PDT began with the studies at the Mayo Clinic in 1960 by R. L. Lipson and S. Schwartz, who observed that injection of crude preparations of hematoporphyrin derivative (HpD) led to fluorescence of neoplastic lesions (9).

Clinical application of PDT using HpD in cancer therapy began at Roswell Park Cancer Institute in 1976 by Dougherty's group. Since 1993, regulatory approval for PDT involving use of a partially purified, commercially available hematoporphyrin derivative compound (Photofrin) in patients with early and

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advanced stage cancer of the lung, digestive tract and genitourinary tract has been obtained in Canada, France, Germany, Japan, the United States and the Netherlands (10).

Photodynamic therapy is now a widely recognized treatment for solid malignant tumours. Over the past 30 years, clinical protocols for numerous cancers have been developed including cancers of the head and neck region, bladder, gastrointestinal tract, lung, and skin cancer (11). To apply PDT more widely for tumours of different localization and histology, specific problems arise that require individual approach. For this purpose PDT is more widely combined with other methods applied in cancer treatment, new methods of PDT are also being created (12, 13).

The Institute of Oncology of Vilnius University (VUOI) has collected quite a considerable experience in PDT. The first experimental research in PDT was started in 1985 (14). In 1989, we were the first in the former USSR and in the first ranks in Eastern Europe to introduce photodynamic treatment in a clinic. In 1993, the Laboratory of Laser and Photodynamic Therapy was founded with clinical and experimental departments at the Lithuanian Oncology Centre. It has been the only clinical laboratory of photodynamic therapy in the Baltic States (15).

Every year hundreds of patients are treated using various PDT methods (16, 17).

Since 1999, regulatory approval for PDT involving use of HpD and ALA in patients for the treatment of primary and recurrent solid tumours in Lithuania has been obtained (18).

The goal of this work was to investigate and to enlarge the possibilities of a comparatively new treatment method, PDT, in clinical radical and palliative treatment of cancer patients. To achieve this, we suggest new effective PDT methods which we created and/or improved, according to the advance of tumorous process, tumour histological form, localization and size.

## MATERIALS AND METHODS

### Clinical characteristics of the patients

The total of 848 patients with both 1435 malignant and 446 precancerous tumours underwent photodynamic therapy in VUOI. There were 724 cancer patients and 124 patients for whom benign tumours such as condylomas, laryngeal papillomatosis, actinic keratosis or *Ca in situ* were estimated. The morphological verification was provided in all the cases until the treatment. Table 1 presents the distribution of morphological types of malignant tumours treated by us with PDT.

Our first PDT experience was in the treatment of patients with advanced cancer of head and neck. In most of these cases PDT was used only as palliation. Favourable results of PDT have

Table 1. Distribution of morphological types of malignant tumours treated with PDT

Tumour morphology	Number of tumours
Squamous cell carcinoma	356
Basal cell carcinoma	461
Melanoma	509
Adenocystic carcinoma	27
Sarcoma	22
Adenocarcinoma	52
Others malignancies	8
<b>Total:</b>	<b>1435</b>

encouraged us to utilize this treatment as the radical treatment modality for residual and even for primary malignant tumours of head and neck, trachea, bronchi, vulva. An especially successful effect was noticed using PDT in the treatment of malignancies located in ocular adnexa and in the ear and *meatus acusticus*.

### Photosensitizers

Hematoporphyrin derivatives (HpD) group photosensitizers such as Photogem (OOO Photogem, Moscow, Russia), Photofrin (QLT PhotoTherapeutics, Vancouver, Canada) and Photosan (Medac GmbH, Hamburg, Germany) were used by us. HpD was applied via intravenous injection with a subsequent irradiation after 24–72 hours with red light ( $\lambda = 630 \pm 3$  nm) at the dose of 200–300 J/cm<sup>2</sup>. Applying PDT, the light power density used by us varied from 25–50 mW/cm<sup>2</sup> for melanoma to 300 mW/cm<sup>2</sup> for basal cell cancer. Usually, we used 200 mW/cm<sup>2</sup> light power density.

Since 1998, the new PDT modality – topical ALA-mediated PDT – was started in the Lithuanian Oncology Centre. At first, it was used only for the treatment of malignant skin and mucosal lesions, later on, ALA-PDT involved some types of premalignant and even benign skin and mucosal lesions, too. We used 5-aminolevulinic acid (ALA) which was produced by Medac GmbH (Hamburg, Germany), and in some cases the ALA methyl ester (Metvix, PhotoCure ASA, Oslo, Norway) was applied. The 20% ALA cream was prepared before administration. It was applied on the cutaneous and mucosal lesions in a thick layer (0.5 ml/cm<sup>2</sup>), under occlusive dressing and kept for 3–5 hours before the red light ( $\lambda = 635 \pm 3$  nm) irradiation. The total dose of absorbed light energy usually was 200 J/cm<sup>2</sup>. The response to the therapy was assessed by morphological examination (for all lesions) and by visual inspection.

### Light sources and light dosimetry

Helium-neon laser was the first used by us (Table 2). However, the power of this laser was very limited, and the duration of the tumour irradiation lasted 10–30 hours. Later on, copper vapour-pumped dye and gold vapour lasers were used by us. Both these lasers are able to deliver light at irradiance up to several hundred mW/cm<sup>2</sup>. These lasers were coupled to optical fibres and used for endoscopic PDT such as in oral cancer, in head and neck cancer, in central lung cancer, in *meatus acusticus* and others. Since 2000, the Lithuanian diode laser ( $\lambda = 635 \pm 3$  nm) was given to us. And in 2006, a new source – light emitting diode (LED) – was acquired by us. LEDs are practicable in the treatment of large tumours of skin and soft tissues.

New and effective PDT methods were created and / or improved by us according to the advance of tumorous process, tumour histological form, localization and size:

1. PDT combined with Nd:YAG laser destruction when treating large tumours and the ones settled in the locations difficult to reach.
2. Long-term multistage low power photosensitized melanoma irradiation, gradually increasing the power of light, applying PDT for skin and mucous melanoma.
3. Intra-arterial PDT for the treatment of locally spreading oral cancer.

Table 2. Specifications of light sources used by us

Laser type	Wavelength (nm)	Timing of radiation (wave)	Maximum power on the tip of fibre (W)
Nd : YAG (neodymium ions in crystals of yttrium-aluminum-garnet)	1064	Continuous pulsed	64
Dye (rhodamines and oxazines) laser pumped with copper vapour laser	630	Quasi continuous	0.3–1
Gold vapour laser	629	Pulsed	1.0
Helium-neon (gas) laser	633	Continuous	0.05
Diode laser	635	Continuous	0.2
Diode laser	633	Continuous	0.31
LED (light emitting diode)	635	Continuous	0.03

### Nd : YAG laser destruction together with PDT

The visible light, which is used for the activation of photosensitizer, penetrates the tissue by less than 2 cm. If the tumour is large, PDT alone is only the palliative method of treatment. Nd : YAG laser evaporation of a big size tumour before PDT allowed to provide the radical treatment. This method was applied for patients with large tumours (the thickness of the tumour was 2 cm or more), for patients with multiple tumours, when the general size of malignancies was 70 cm<sup>2</sup> or more, and for patients with the tumours settled in the locations difficult to reach. For these patients the surgical lasers were used (the power on the tip of fibre was 20–50 W) in order to remove the tumour mass. After 1–7 days had passed, the usual PDT treatment was given. The total of 557 patients (956 tumours) have got Nd : YAG laser surgical treatment prior to PDT.

### Photodynamic therapy of melanoma

A new method of PDT – a long-term multistage low power photosensitized melanoma laser lighting, gradually increasing the power of the light was applied for 51 patients with multiplex metastatical melanoma (509 tumours) in skin, mucous and soft tissue. On the first day after HpD injection, melanoma was irradiated with a low power (30–50 mW) red light. The light power density was 20–50 mW/cm<sup>2</sup>. On the first day 1/4 part of the absorbed total light energy by melanoma (100 J/cm<sup>2</sup>) was realized. After that, when the first changes in the malignancy began: tumour colour changes, moisture, oedema, usually it happened next day, the tumour was irradiated with 75–100 mW power red light. The light power density was 75–100 mW/cm<sup>2</sup>. Next day 1/2 part of the total absorbed light energy by melanoma was realized. It was about 200 J/cm<sup>2</sup>. The remaining 1/4 part of the absorbed light energy was applied on the third day after HpD injection, when melanoma was irradiated with 150–300 mW power red light. The light power density was 150–300 mW/cm<sup>2</sup>. The total of 400 J/cm<sup>2</sup> of the absorbed light energy was realized.

### Intra-arterial PDT

While applying PDT for oral cancer patients, it is possible to inject a photosensitizer into the artery branch supplying the tumour. For that purpose there was a cannula installed into the artery *temporalis superficialis*. The instalment depth was defined by the injection of methylen blue dye through the cannula. When tumour tissues were coloured in blue, the cannula was fixed at the skin of preauricular region. Later HpD (10–50 mg) was injected through this cannula and soon after that the tumour was irradiated with red laser light. The dose of HpD and the time of light exposition depend on the size of the tumour. The absorbed

light energy by tumour was 200 J/cm<sup>2</sup>. Next day after the red light irradiation necrosis of tumour tissue was noticed. If it was not full, we repeated laser irradiation. Two days later, intra-arterial (i/a) PDT morphological tumour site tissues examination was performed. If there was no clinical and morphological evidence of the tumour, the cannula was removed. 24 patients with 30 oral malignancies were treated with i/a PDT by us. PDT was applied as a radical method for 20 patients, while for 4 patients it served as a palliative method of treatment. These patients formed an investigative group. There was a control group which consisted of 56 patients with 60 foci of oral cancer for whom ordinary PDT was provided.

### Differences of photodamage in various malignant tissues

To estimate the dependence of PDT efficiency and pathomorphological differences of photodamage in various malignant tissues on the histological type of tumour and on the differences in the light power and light exposition used, careful cytological tumour tissues studies were performed for each malignant lesion before PDT, during PDT, immediately after PDT, 6 h, 24 h, 48 h after PDT and on 4th, 10th or 14th day after PDT.

Histological tissue examination for most malignancies was provided before PDT and on 7th, 14th day after PDT. In the case of melanoma, histological examination was provided only once on 7–10th day after PDT, when wide melanoma excision was performed.

During morphological tumour examination, the main attention was paid to the nature of photodamage in a cell membrane, nucleus, and chromatine and to the changes in the surrounding healthy tissues. It was important to establish the time at which necrobiosis and necrosis appear in each histological type of tumour.

### Statistical data analysis

For data analysis the program package SAS (Statistical Analysis Systems) was used. In particular, simple descriptive statistics, frequency tables were obtained by means of the procedures FREQ, MEAN. To compare the results we used Student's and Fisher's criteria for continuous data and X<sup>2</sup> criterion for rank data.

## RESULTS

The immediate result of PDT depended on the thickness of the malignant tumour treated. If the thickness of the tumour was less than 4 mm, the single PDT course was sufficient for the complete tumour regression. Malignant melanoma was an exception. It required a special PDT method. While providing



adequate PDT, there were only slight differences in the immediate response of tumours of various histogenesis observed. However, the usual PDT is more effective in basal cell cancer than in squamous cell carcinoma or in other malignancies.

There was no difference in the effectiveness of PDT in primary and recurrent lesion as well as in primary untreated tumour and the ones, for which radiotherapy or chemotherapy was provided (Figs. 1, 2). In most of the cases, when there was no complete response, PDT was repeated. However, the second course of ordinary PDT can be repeated only in 1 month. It depends on the HpD retention in some types of tissue. Topical ALA-mediated PDT can help to tackle this problem partially. In the cases when the ALA-PDT effectiveness is insufficient we can repeat the treatment next day again, insofar as it is needed.

ALA-PDT can be provided immediately after the ordinary PDT, too. In our experience (52 malignancies underwent this treatment), such type of treatment is even more effective than two topical ALA-mediated PDT courses applied one by one.

From 1998 to 2007, the total of 271 patients with both 317 malignant and 209 precancerous tumours underwent ALA-mediated photodynamic therapy in VUOI.

After a single ALA-PDT treatment, 164 (91%) basal cell carcinomas, 63 (75%) squamous cell carcinomas and 30 other tumours (63%) showed a complete response, for the remaining 60 lesions, a partial response was observed, indicated by a marked reduction of the tumour size (Table 3). In most of these cases the PDT was repeated.

There was no visible scar or pigmentation formation in any case. PDT with topically applied ALA has been shown to be

Table 3. ALA-PDT results in the treatment of malignant tumours

Morphology	Number of tumours	Regression of tumours	
		100%	≥75%
Squamous cell carcinoma	87	63	24
Basal cell carcinoma	182	164	18
Adenocystic carcinoma	7	5	2
Adenocarcinoma	12	10	2
Melanoma	3	–	3
Lentigo maligna (melanoma <i>in situ</i> )	2	–	2
Carcinoma <i>in situ</i>	16	11	5
Sarcoma	8	4	4
<b>Total:</b>	317	257	60

highly effective in the treatment of skin and mucosal lesions. The excellent cosmetic effect was noticed in all the cases. Superficial basal cell carcinomas (BCC) respond very well to topical ALA in combination with light, however nodular BCC responds less favourably to ALA-PDT as a single treatment. For nodular BCC, ALA-PDT has been shown to be a valuable adjuvant therapy in combination with surgical Nd : YAG laser destruction. Both superficial and nodular squamous cell cancer were less responsive than BCC to ALA-PDT, but complete remission has been achieved using multiple sessions with high light doses.

Irradiation of sensitized skin causes erythema and mild burning sensation within the treatment field. Erythema and mild oedema in all the cases were less, than the ones following the usual intravenous PDT treatment. Selective tumour necrosis

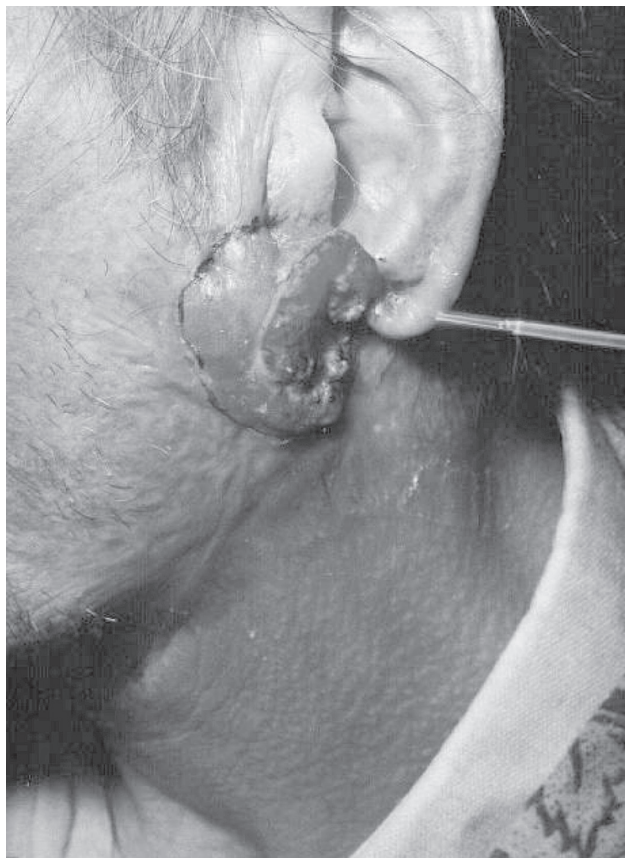


Fig. 1. Metastatical adenocarcinoma during photodynamic therapy



Fig. 2. Metastatical adenocarcinoma 2 days after photodynamic therapy

occurred within 1–7 days. Healing was usually complete within one week. Cosmetic results are considered to be good or better than after other treatments, including surgery and cryotherapy.

All 214 patients which malignancies underwent ALA-PDT were followed-up by us for the period of 5 to 108 months. During this period recurrences were established in 32 patients. In most cases these were the patients with recurrent disease T<sub>3-4</sub>. Tumour thickness determines therapeutic response to PDT: all BCC thinner than 1 mm cleared after a single treatment with ALA-PDT, although 4 late recurrences in respectively 18, 22, 38 and 57 months were observed. In contrast, none of the BCC thicker than 3 mm responded to single PDT treatment completely. For nodular BCC, a significant increase of complete response (CR) can be achieved, when ALA-PDT is combined with partial tumour debulking by surgical laser destruction. CR rates >90% were obtained when PDT was performed either immediately after curettage or 3 weeks after tumour debulking. The same data were reported by others authors (19).

Topical ALA-PDT has been applied to treat squamous cell carcinomas (SCC). Superficial as well as nodular lesions, SCC are less responsive to ALA-PDT as compared to BCC using identical treatment protocols. Superficial SCC show better responses than nodular SCC. High light doses are more effective as well as repeated treatment. The best effect was noticed in cases when ALA-PDT of SCC was combined with partial tumour debulking by Nd : YAG laser destruction.

#### Nd : YAG laser destruction together with PDT

Nd : YAG laser destruction together with PDT was used in the radical treatment of all the malignancies (except melanoma) the thickness of which exceeded 3 mm, when it was possible. In cases when there was no possibility to provide Nd : YAG laser destruction prior to PDT, both the immediate and distant results were worse. It was statistically approved by us. However, in case of T<sub>3</sub>-T<sub>4</sub> tumours Nd : YAG laser destruction alone is often insufficient for the full removal of malignancy. So Nd : YAG laser destruction together with PDT is the method of choice and must be used in all the cases (except malignant melanoma) when the thickness of the tumour is 2 cm or more and in most of the cases when the thickness of the tumour exceeds 3 mm. It enables to provide radical PDT treatment for a number of patients with large tumours and with the tumours in the location difficult to reach.

#### Results of melanoma PDT

Providing PDT full melanoma necrosis usually occurs only on 7–10th day after the PDT. In cases when PDT is provided for the treatment of multiplex metastatical lesions a well marked oedema of the surrounding tissues appears. The immediate results of melanoma PDT depends on the thickness of the tumour. When it was less than 22 mm, usually a complete response was noticed. The immediate results of recurrent melanoma PDT are presented in Table 4.

All the patients with recurrent melanomas were followed up for the period of 1 month (the patient had died) to 16 years. The median follow up was 21 months. As the distant result of melanoma PDT, the remission of the disease was established in 35 patients. 17 of them were alive and well for the period of

Table 4. The immediate results of recurrent melanoma PDT

Necrosis of melanoma	Number of tumours
Full (100%)	402
Significant ( $\geq 75\%$ )	10
Partial ( $\geq 50\%$ )	91
Slight ( $\leq 0\%$ )	6
<b>Total:</b>	<b>509</b>

12–121 months. Fig. 3 represents the multiplex lesions of metastatical melanoma. The same patient 4 years after PDT – there is no evidence of melanoma (Fig. 4). At present 7 of them are without melanoma for the period of: 16 years and 14 years, 104, 60, 41, 40 and 15 months. The median survival of patients with recurrent melanoma (for whom PDT was applied) from the moment of finding of recurrence was 27 months. PDT was effective even for the patients with multiplex cutaneous and subcutaneous lesions. For example, the patient with 214 cutaneous and subcutaneous metastatical lesions after 2 PDT courses was alive and well for the period of 8 months.

#### Intra-arterial PDT

As a result of intra-arterial PDT, 9 patients (10 lesions) have fully recovered. For other 15 patients the treatment was repeated. After the second PDT treatment full necrosis of cancer was observed in 8 patients (11 malignancies). For 2 patients (2 cancer



Fig. 3. Multiplex lesions of metastatical melanoma until photodynamic therapy



Fig. 4. The same patient 4 years after PDT – there is no evidence of melanoma

foci) ~70% of tumour regression were noticed. For 2 patients (2 cancer foci) 75% of tumour regression and for the other 2 patients (4 malignancies) ~30% of tumour regression was noticed. For the last patient no evidence of tumour macroscopically was observed, but some tumour tissue was noticed during morphological examination (Table 5).

Table 5. Comparative results of ordinary and i/a PDT in oral cancer

Group	Number of treated tumours			
	Tumour disappeared %	Regression		
		≥75%	≥50%	<50%
Intra-arterial PDT	21(70%)	3(10%)	2(7%)	4(13%)
Ordinary PDT	30(50%)	12(20%)	14(23%)	4(7%)

All the patients for whom i/a PDT was provided were followed up for the period of 12 months to 8 years. The average follow-up was 32.5 months.

56 patients (60 tumours) for whom ordinary PDT was provided were followed up for the period of 10 months to 5.5 years. The average follow-up was 28.4 months. There were recurrent or metastatical diseases in 30 of the patients. In 12 of them it caused death. 11 patients are alive and well. For the rest of the patients remission was established. The data processed statistically revealed that in both – i/a PDT and ordinary PDT – groups the immediate and distant results are not diverse.

#### Differences of photodamage in various malignant tissues

Applying PDT for 1435 malignant tumours of different histogenesis we noticed that first destructive changes were found in basal cell carcinoma cells. In most cases complete necrosis of these cells was observed immediately after PDT (33% of tumours) or 6–12 h after PDT (46% of tumours). In some lesions (21%) necrosis was noticed later, but no more than 48 h after PDT. There was no any morphological change in a squamous cell carcinoma and adenocarcinoma tissue immediately after PDT. Complete destruction of squamous cell cancer usually was observed on 2nd–4th day after PDT (95% of tumours). Adenocarcinoma had necrotized completely on the 2nd–3rd day after PDT (97% of tumours). Applying PDT to melanoma, first changes are observed on the first day: chromatin in some melanoma cells becomes rougher, reticular and thinned, however, full melanoma necrosis in most cases was observed on the 7–10th day after PDT.

#### Premalignant and benign tumours PDT

While applying PDT for 124 patients with 446 premalignant and benign tumours, we noticed that the effectiveness of this treatment depends on the morphological type of the tumour. There was no statistically significant difference between the immediate and distant results of topical ALA-PDT and ordinary PDT.

Laryngeal papillomas, condylomas and Ca *in situ* were the most sensitive to PDT. Table 6 presents immediate results of PDT in benign tumours. The full necrosis of laryngeal papillomas and condylomas was evident on the very next day, providing PDT both ordinary and ALA-PDT. PDT was effective in the treatment of Ca *in situ* when it was localized in skin or mucous (vulva, oral region). However, there was no effect in the treatment of melanoma *in situ* and moles.

Table 6. Immediate results of PDT in benign tumours

Tumour morphology	Complete response	Partial response	No response
Leucoplakia	15	8	3
Erythroplasia	4	3	1
Condylomas	20	10	–
Laryngeal papillomas	60	7	1
Carcinoma <i>in situ</i>	40	15	–
Actinic keratosis	20	30	7
Atypical dermatitis	23	14	1
Morbus Darrieux	5	1	–
Psoriasis	4	7	1
Cicatrix	–	2	8
Keratoacanthoma	–	1	2
Trophical wounds	1	17	2
Moles	–	–	84
Other	2	16	10

Applying PDT to 84 active moles, non-abundant lymphocytic infiltration was sometimes observed in derma during histological examination, but there was no evidence of necrosis in any of them. All the moles treated with PDT 5–10 days after PDT underwent adequate excision. In the treatment of scars PDT was ineffective either. The effectiveness of psoriasis PDT depends on the thickness of lesion.

To sum up, we can state that photo biological changes after PDT depend on the tumour histology type. The earliest photo biological changes start in basal cell cancer, and the latest ones in atypical melanophores. PDT has only slight influence on melanoma *in situ* and healthy mole tissue.

#### DISCUSSIONS

The data presented in this article have shown that photodynamic therapy is easily tolerable by cancer patients, while applying it both in radical and palliative treatment. PDT is effective in primary and recurrent lesion as well as in primary untreated tumour and the ones for which radiotherapy or chemotherapy was provided. The majority of studies devoted to PDT confirm our results (1, 2, 4, 6, 7, 10, 11, 13, 19). PDT is effective even for tumours which are resistant to radiotherapy and / or chemotherapy, or the ones the treatment possibilities for which have already been used up. However, the scientists from Pennsylvania Medical Centre do not recommend PDT for patients with upper aerodigestive tract carcinoma who have received prior treatment with a combination of external beam radiotherapy and intraluminal brachytherapy because it seems to be at higher risk for complications (20).

PDT produces a complete response in a very high percentage of patients, and the frequency of follow-up treatments is no greater than the one found out with other treatment modalities. One of the suitable PDT characteristics to be applied in oncology is that all the histological types of tumour except melanoma are sensitive to this treatment, so this encourages the investigation of the method on a broader scale. High level of porphyrins is noticed in tissue of melanoma, therefore PDT of melanoma is hopeful. However, a large number of scientists certify that the results of skin melanoma PDT are poor (2, 5, 13, 19). To our mind, during an ordinary PDT 24–48 h after the injection of a



photosensitizer, melanoma, like other skin tumours, is irradiated with 300 mW red light, light power density 300 mW/cm<sup>2</sup>. At the beginning of such irradiation the superficial necrotic "armour" appears. Through this "armour", light penetration to a deeper tissue of melanoma becomes difficult. So it is impossible to achieve full necrosis of melanoma tissues. To avoid this phenomenon, a specific PDT method for melanoma was proposed by us: "multi-stage low power photosensitized melanoma laser lighting, gradually increasing the power of the light". This method makes full skin and mucous melanoma necrosis possible and significantly improves distant treatment results.

We agree with the point of majority of field scientists (1, 2, 6, 7, 11, 13) that PDT can be employed as a successful treatment for non cancerous conditions such as actinic keratosis, psoriasis and local viral disease: laryngeal papillomas and condylomas.

While providing PDT we noticed that there were significant response differences of tumours of various histogenesis. PDT has only slight influence on melanoma *in situ* and healthy mole tissue, but it was highly effective in the treatment of laryngeal papillomas, condylomas and Ca *in situ*. On the other hand, there were some differences in PDT results, when we used low power laser light and higher power laser systems. In spite of that, the absorbed light energy in both cases was the same.

As regards our data, the topical ALA-PDT is simpler for a patient (it can be provided as outpatient therapy) than the common PDT. This treatment can be repeated next day again, insofar as it is needed. Similar results are presented by other authors (2, 4–6, 12, 13, 19).

The new PDT method – intra-arterial PDT in head and neck cancer – proposed by us may serve as an alternative to ordinary PDT, because comparison of *i/a* PDT results versus ordinary PDT results showed equal effectiveness of these treatments. On the other hand, *i/a* PDT makes the expenditure on expensive photosensitizers much lower. Patients need not to be protected from the sunlight. *I/a* PDT also enables to apply effective but fast splitting photosensitizers which are difficult to use in the usual PDT. The suggested *i/a* PDT of oral cancer can be applied as a model when implementing *i/a* PDT to tumours of other localizations.

#### Adverse treatment effects

The most common adverse effect of conventional PDT sensitizers is prolonged skin sensibility to sunlight and ultraviolet light. Patients who received HpD group sensitizers such as Photofrin, Photosan and Photogem must avoid exposure of skin and eyes to direct sunlight, ultraviolet light and even bright indoor light including dental lamps and operating room lamps for about one month. There were photosensitivity reactions such as oedema and erythema of the face and hands in 35 patients who had not protected their skin enough from the direct sunlight. This complication was more common in patients who underwent multiplex courses of PDT.

Topically applied substances such as ALA or Metvix theoretically are free from this disadvantage, but in reality the site of the skin which underwent topical ALA-PDT must be protected from the sunlight and ultraviolet light for 2–4 days. The well-marked erythema had appeared on the face of the patient who had spent 3 hours in his car without any dressing of the treated lesion next day after topical ALA-PDT.

The most threatening adverse effect – anaphylactic shock – was estimated in one patient 2 min. after the beginning of *i/v* infusion of HpD. The infusion was immediately stopped and adequate treatment was provided (including injection of dexamethasone and infusotherapy) with good outcome. It was the first HpD injection for this patient. And there was no any other allergic reaction noticed during all his treatment. Our hypothesis is that such anaphylactic reaction could be caused by multiplex blood transfusions which were provided 10 years ago. Usually PDT is a well-tolerated method of treatment, and, from 1986 to date, we have found only one publication – a case report of an acute urticarial type hypersensitivity reaction immediately following the injection of HpD (21).

#### CONCLUSIONS

Photodynamic therapy is effective in primary and recurrent lesion as well as in primary untreated tumour and the ones for which radiotherapy or chemotherapy was provided. PDT is also effective for tumours which are resistant to other treatments. PDT-induced photobiological changes depend on the tumour histology type. PDT was highly effective in the treatment of laryngeal papillomas, condylomas and Ca *in situ*, too. However, topical ALA-PDT is simpler for patients. PDT combined with Nd : YAG laser destruction makes radical treatment possible to large tumours of difficult-to-reach localizations, otherwise a single PDT would be only palliative.

Multistage low power radiation of photosensitized melanoma gradually increasing light power makes full skin and mucous melanoma necrosis possible, and significantly improves distant treatment results.

Intra-arterial PDT makes expenditure of expensive photosensitizers much lower and enables to use effective but fast splitting photosensitizers which are difficult to use in the usual PDT. The effectiveness of *i/a* PDT is equal to the one of the ordinary PDT.

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#### PIKTYBINIŲ IR GERYBINIŲ NAVIKŲ FOTODINAMINĖ TERAPIJA LIETUVOJE

##### *Santrauka*

Šio darbo tikslas buvo ištirti ir praplėsti fotodinaminės terapijos (FDT) radikalaus ir paliatyvaus gydymo galimybes klinikoje. Piktybiniai ir gerybiniai navikai buvo gydyti taikant 6 skirtingas lazerines sistemas ir naudojant skirtingus fotosensibilizatorius: i/v leidžiamus hematoporfirino darinius (HpD) bei ant naviko tepamą 5-aminolevulininę rūgštį, dėl kurios audiniuose susidaro protoporfirinas.

FDT pritaikėme 848 ligoniams 1435 piktybinių ir 446 gerybinių navikų gydymui. Po vieno FDT kurso visiškai išnyko 91% bazaliomų, 75% plokščialąstelinio vėžio ir 63% kitų piktybinių navikų. FDT buvo efektyvi gydant ir kai kuriuos gerybinius darinius: gerklų papilomatozę, kondilomas, aktinines keratozes. FDT yra lengvai ligonių toleruojamas efektyvus gydymo metodas gydant tiek pirminius navikus, tiek recidyvus, kuriems prieš tai jau taikyti kiti gydymo metodai. Skirtingos histogenezės navikams tikslinga taikyti skirtingas FDT modifikacijas.

**Raktažodžiai:** fotodinaminė terapija, lazeriai, hematoporfirino dariniai, 5-aminolevulininė rūgštis