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Possibilities of Laser Spectroscopy Methods for Prediction of the Radiotherapy Results

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Abstract

In this paper, possibilities of laser fluorescence spectroscopy to predict the reactions of the oral cavity cancer to radiation treatment are considered. A theoretically substantiated assumption about the link between the tumor's consumption of an exogenous photosensitizer and its radioresistance is proposed. The first experience with the use of the Radahlorin photosensitizer is described; preliminary results of the 5 patients study are presented. As a result different photosensitizer consumptions versus different treatment outcomes are discussed.

Keywords: laser fluorescence spectroscopy, photosensitizer, oral cavity cancer, radiotherapy, cross-resistance

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1. Introduction

Statistical analysis of malignant neoplasms in Russia has shown that more than 11,000 people per year fall ill with squamous cell carcinoma of the oral mucosa, and the mortality rate due to this pathology in the first year from the moment of diagnosis is about 45% [1]. In the world practice, various methods of radiotherapy, surgical and combined treatments are proposed and used to cure patients suffering from locally advanced forms of oral cavity cancer. However, in general, the results of the treatment are unsatisfactory, in a view of low survival rates. According to statistics, more than 300 thousand cases and 145 thousand deaths caused by oral cancer were recorded in the world in 2012 [2].

It is known that the reason for low survival rates is a resistance of tumor cells to such damaging factors as chemotherapy and ionizing radiation. Despite the evidence of cross-resistant of tumor cells of different histogenesis, in a number of cells' sublines

it was not discovered [3]. In addition, for some sublines, the resistance of cells to one damaging factor increases the sensitivity to other ones [3]. Despite the existence of a numerous investigations in which known mechanisms of cross resistance (both multidrug resistance (MDR) and pleiotropic resistance i.e. the resistance to factors of different nature) [3] were described, in a view of the complexity and multifacetedness of this phenomenon, the problem of its study remains relevant for today [4].

In a number of clinical cases, when the efficacy of radiotherapy and chemotherapy is low, clinicians leads to a less common type of therapy, to a photodynamic therapy (PDT) for example [5]. PDT is a type of phototherapy with the use of three components: tumor-localized photosensitizer (PS), light and tissue oxygen, to initiate phototoxic reactions in the tumor [6]. Therefore, the activity of PS consumption by the tumor is a condition determining the effectiveness of PDT. For a long time the mechanisms of tumor PDT resistance believed not to be associated with mechanisms of resistance to other therapies [5]. But recent studies have shown the fallacy of these judgments. In the reference [7] the mechanisms linking MDR and the PS consumption by tissues are described. Therefore, in this paper, it was suggested that the data on the PS fluorescence in tumors could carry information about the presence of MDR or a radioresistance.

2. Materials and Methods

Five patients with stage II-III cancer participated in the preliminary experiment. Fluorescence spectra of the exogenous photosensitizer Radahlorin ("RADA PHARMA" LLC, Russia), also known as Bremachlorin, were investigated in the field of pathology and intact area. Characteristics of patients are presented in Table 1.

Table 1: Characteristics of patients.

Patient	Age	Gender	Diagnosis
N.T.A.	60	female	Cancer of the floor of mouth $T_2N_0M_0$
T.S.I.	60	male	Cancer of the floor of mouth $T_2N_0M_0$
S.S.B.	57	male	Cancer of the oral tongue $T_2N_0M_0$
K.Y.M.	53	male	Cancer of the floor of mouth $T_2N_0M_0$
D.A.V.	58	male	Oral of the floor of mouth extended to alveolar process $T_3N_0M_0$

Prior to each study, a photosensitizer "Radahlorin" was injected by intravenous drip infusions for 30-40 minutes at a standard dosage of 0.5-0.6 mg/kg. Three hours after

the Radahlorin injection, when, the contrast index has to reach a maximum according to PS pharmacokinetics [8], the fluorescence spectra from the tumor and of the intact region were measured using the LAKK-M diagnostic system [9].

All diagnostic data were collected using a flexible optical fiber. Its distal end was in contact with the surface of the patient's mucosa. Excitation of tissue fluorescence was made in the continuous wave (CW) mode at the wavelength 635 nm (a semi-conductor laser). Power of the laser radiation from the distal end of the optical fiber probe (on a surface of tissues) was around 5 mW. Registration of the fluorescence flux was carried out in the waveband 650-700 nm by the built-in fiber optic spectrometer with the CCD detector, which is included in the system design. Fluorescence intensity was measured at λ_f = 670 nm - in a maximum of the fluorescent spectrum of the used photosensitizer «Radahlorin». Hereinafter, the intensity at this wavelength will be called "fluorescence intensity" and be indicated by I_f.

All measurements of the Radahlorin spectra were carried out before and during the remote gamma-therapy performed according to the Dynamic Multifractioning Schedule (DMS) of the radiation doze [10]. Within the first three days, a tumor was irradiated daily by 3.5-4 Gy until the total dose of 10.8 Gy was reached. During the next 10 days irradiation was carried out twice a day at 1 Gy at the interval of 5 - 6 hours until the total dose of 34.8 Gy was reached. After 10-14 days, after reduction of side effects, the second half of the split course was carried out according to a similar scheme. A total dose was 60 Gy (120 TDF units) (Fig. 1). From the diagnostic point of view the beginning of the second stage of irradiation is a very important step in DMS. On this step a doctor must formulate a final decision of the efficacy of applied therapy – to have to continue it or not [10]?

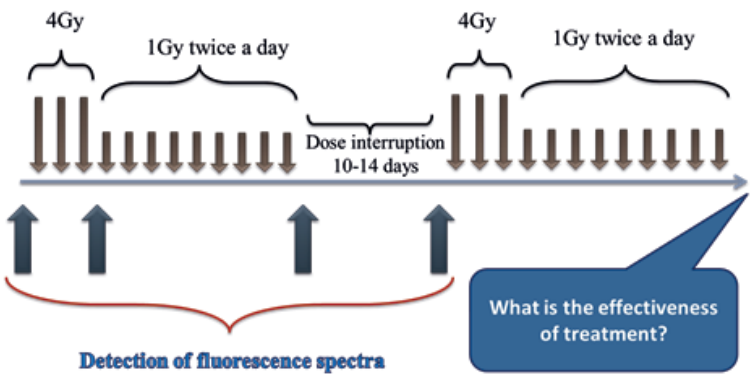

Figure 1: Design of the experiments for each patient.

Obtained optical data were compared with the clinical observations of the preliminary intermediate treatment results estimated by evaluation of the size of the

residual tumor after the dose interruption in the DMS. To quantify the fluorescence, the relative fluorescence intensity index of the tumor $\mu(\lambda_f)$ was calculated by the following formula [11]:

$$\mu(\lambda_f) = \frac{I_f(\lambda_f)}{I_{f0}(\lambda_f)} \quad (1)$$

where I_f is the fluorescence intensity from the tumor, I_{f0} is the fluorescence intensity from the intact region, and λ_f = 670 nm is the fluorescence wavelength. All of the above parameters were recorded at several points from the visible tumor surface and from the intact tissues for each patient. All measured data were averaged over these points for leveling the effect of tumor surface heterogeneity. For example, for I_f, recorded at several (N) points on the tumor surface, the final diagnostic parameter was as follows:

$$I_f = \frac{1}{N}\sum_{i=1}^{N} I_f(i) \quad (2)$$

where: $I_f(i)$ is the intensity measured at a certain point on the surface of the tumor or intact area, N is the number of such points.

The diagnostic system "LAKK-M" has all certificates which are required in Russia to be used in any real clinical situation. All the studies were conducted in the Laser Diagnostic Room of the Radiology Department in accordance with the Sanitary Norms and Rules for the Design and Operation of Lasers (SanPiN No. 5804-91) with the weak scattered daylight and the absence of bright external sources of optical radiation in the room.

3. Results

Examples of the fluorescence spectra of Radahlorin detected from a tumor and on intact region are shown in Fig. 2.

The first experience results on the 5 patients' examinations and the immediate results of their treatment are presented in Table 2.

The mean value of the deviation of the function $\mu(\lambda)$ (Eq.1) are indicated in the Table 2.

Nearest treatment outcome did not evaluated yet due to the needed 3-month rest period. It will be done and described in our next publications.

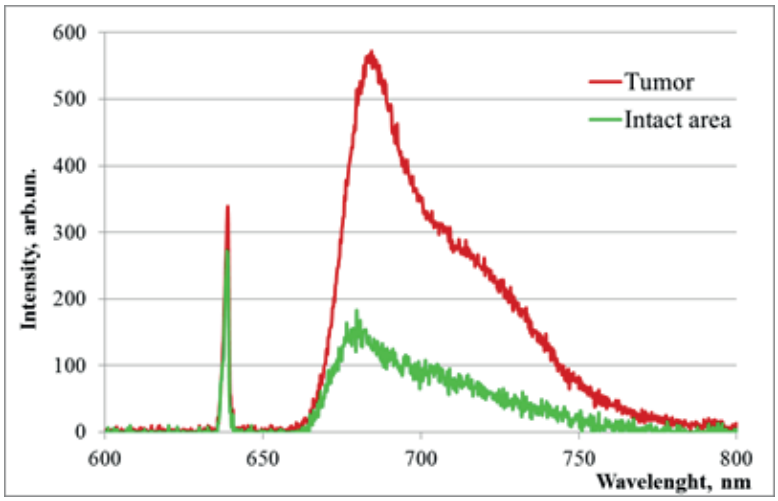

Figure 2: Fluorescence spectra of Radahlorin detected at total dose of 10.8 Gy for patient D.A.V.

Table 2: $\mu(\lambda_f)$ and the percentage of the residual tumor for 5 patients.

	$\mu(670)_{\text{Before}}$ rel.un.	**$\mu(670)_{10,8\,Gy}$ rel.un.**	**$\mu(670)_{34,8\,Gy}$ rel.un.**	**$\mu(670)_{\text{Before the 2nd stage}}$ rel.un.**	**Rest tumor$_{\text{Before the 2nd stage}}$ %**
N.T.A. Cancer of the floor of mouth $T_2N_0M_0$	1,0±0,1	1,4±0,1	0,8±0,2	1,1±0,2	40
T.S.I. Cancer of the floor of mouth $T_2N_0M_0$	1,51±0,13	1,13±0,02	0,69±0,02	0,79±0,02	10
S.S.B. Cancer of the oral tongue $T_2N_0M_0$	1,7±0,6	1,4±0,6	0,6±0,2	0,8±0,4	50
K.Y.M. Cancer of the floor of mouth $T_2N_0M_0$	1,0±0,3	1,1±0,3	0,8±0,2	1,2±0,3	40
D.A.V. Oral of the floor of mouth extended to alveolar process $T_3N_0M_0$	1,3±0,2	2,5±0,3	1,4±0,4	0,9±0,2	30

4. Discussion

Our preliminary results did not show obvious correlations between the measured parameters and the intermediate treatment results (Table 2). However, even now, the differences in relative fluorescence indices of tumors reflecting the tumor accumulation activity of the photosensitizer in comparison with the intact tissues are visible for

different patients. Differences in the dynamics of μ(λ) also may reflect the individual reaction of tumors to radiation exposure. For example, a decrease in the μ(λ) at the end of the dose interruption compared with the initial one for patients T.S.I. and D.A.V. is observed. This trend is not tracked for patients with a greater percentage of rest tumor (N.T.A., K.I.M.). Dynamic of μ(λ) for the patient S.S.B can't be correlated with the above one correctly because of the discrepancy between tumor localizations. Therefore, evaluation of parameter dynamic is also important.

Individual features of the tumor, the development of which can be accompanied by inflammatory processes and hypoxia affecting the photosensitizer redistribution in tissues may be the cause of such results [11]. It is also worth noting that radiation reactions of tissues changing optical properties within the diagnostic volume have a great influence on the results. The presence of scar tissue, edema, thick and viscous saliva, or surface erosions lead to a change in the scattering and absorption coefficients averaged over the diagnostic volume. Such changes are also impact on the fluorescence spectrum, namely, on the value of I_f, and, consequently, on μ(λ_f). Accordingly, we can conclude that comparing the study results for patients with different tumor locations is incorrect. It is known that the blood supplies of the tongue tissues, oral cavity tissues and alveolar process are not the same; hence the optical properties of these regions are different. Comparison of tumors at different stages is also incorrect, because their clinical manifestations are not the same [12]. In this case, patients diagnosed with "Cancer of the floor of mouth $T_2N_0M_0$" should become a separate group. The examination results of these patients suggest that the more active the tumor cells accumulate PS before the therapy and the more this activity decreases during DMS, the better result of the treatment is. Perhaps the dynamics of accumulation of PS directly reflects the process of the tumor destruction. To test this hypothesis, all patients need to be divided into groups according to the area of tumor localization and its stages. It is also necessary to study a larger number of patients.

In the future, for the unification of the developed method, which would be valid for different stages of the disease and various localizations of malignant tumors; the fluorescence spectra should be corrected in response to optical properties of the target region. The combination of methods of laser fluorescence spectroscopy and backscattering spectroscopy will help to solve this task. Probing the tissue with a wide-band (white) light source will allow estimating the fraction of light detected by the device and normalized to the exciting light. It is worth noting the importance of use mathematically and physically based algorithms for correction fluorescence spectra, taking into account both the optical tissues properties and the features of the diagnostic system: the distance between illuminating and receiving fibers, their diameter, the

power of the incident radiation, etc. The diagnostic volumes for the measuring of fluorescence and backscattering spectra should be identical, so there is a need for a single diagnostic system combining the physical principles of LFS and backscattering spectroscopy.

5. Conclusion

The possibility of the use of optical diagnostic methods for predicting tumor treatment results was considered. The first experience of studying the exogenous fluorescence of the oral cavity tumor suggested that the more active the tumor cells accumulate the photosensitizer before the radiotherapy, and the more significant this activity falls in the course of treatment, the more effective the therapy. Also, the analysis of the pilot experiment data showed the need to a new diagnostic system that simultaneously implements the principles of laser fluorescence and backscattering spectroscopy.

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