Intraoperational Thermal Control of Perifocal Edema in Photodynamic Therapy of Malignant Brain Tumors

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© **I.A. Medyanik,** MD, PhD, Senior Researcher, Microneurosurgery Group;
M.G. Volovik, MD, PhD, Senior Researcher, Department of Functional Diagnostics;
A.V. Dydykin, PhD Student;
K.S. Yashin, PhD Student;
K.V. Kulakova, PhD, Researcher, Pathological Anatomy Group;
S.N. Bugrov, MD, PhD, Leading Researcher, Pathological Anatomy Group;
N.N. Karyakin, MD, DSc, Director

Privolgzhsky Federal Medical Research Center, 18 Verkhne-Volzhskaya naberezhnaya St., Nizhny Novgorod, 603155, Russian Federation

The aim of the investigation was to assess the role of infrared imaging for brain tissue heating when exposed to laser radiation in photodynamic therapy of removed tumor bed brain, and its effect on postoperative edema.

Materials and Methods. We studied the treatment results of 20 patients with malignant brain tumors with intraoperative photodynamic therapy (PDT). The patients were divided into two groups: the study group (n=12) had intraoperative infrared imaging (IRI)-guided PDT, and the control group patients (n=8) had no IRI control.

Results. Perifocal edema in the study group on the first postoperative day decreased, and was 50.4 [16.4; 79.3] and 88.5 [30.3; 110.6]% of preoperative values according to axial and coronary section study. In the control group postoperative edema increased and was 227.9 [92.4; 303.8] and 154.7 [84.5; 150.3]% of the initial.

Conclusion. PDT is accompanied by temperature rise of the exposed tissues, and increased perifocal edema in an early postoperative period. IRI control of exposed tissues heating in PDT of tumor bed enables to avoid edema augmentation of surrounding brain tissues.

Key words: photodynamic therapy; brain tumors; perifocal edema; infrared imaging; thermal control.

Complex approach to the treatment of malignant brain tumors including microsurgical oncotomy and postoperative chemo-radiotherapy facilitates maximum possible prolongation of patients' life. However, if a gold standard in the therapy of patients with glioblastomas (radiotherapy with simultaneous administration of temozolomide) is used, the mean lifetime is 14.6 months, and when using all most up-to-date techniques in the treatment of anaplastic astrocytomas it is 50.5 months [1, 2].

One of the reasons for that is infiltrative tumor growth into the surrounding brain matter. According to some data, tumor cells are revealed even in another hemisphere [3]. Operative intervention does not provide ablasticity, therefore, the development and application of techniques with a selective effect on tumor cells including photodynamic therapy (PDT) is of current interest now. PDT increases a radicality degree in glioma removal due to the fact that tumor cells are destroyed by the mechanisms, which differ from the effect of chemotherapy or radiotherapy [4], improves long-term results increasing patients' survival [5]. PDT is considered [5–7] to be based on three main mechanisms of action. Firstly, the interaction between light energy (photons) and a photosensitizer selectively accumulated in tumor cells results in the occurrence of free radical compounds, which damage mitochondria, DNA and membranes of tumor cells causing their apoptosis and lysis. Secondly, photochemistry-induced obliteration of tumor vessels results in tumor ischemic necrosis. Thirdly, local immunity is stimulated.

PDT is widely used in brain tumor removal [7–10], however, experimental researches aimed at its efficiency improvement are being carried out [11, 12]. The technique presupposes the exposure over a particular period of time, which is calculated due to several parameters: a tumor size or the area exposed to radiation, laser radiation power, a photosensitizer type. If less estimated time is used, no desirable anti-tumor effect is reached. In neuro-oncology after removing large masses, the necessary estimation exposure time is 40 min. It can result in hyperthermia of surrounding

For contacts: Igor A. Medyanik, e-mail: med_neuro@inbox.ru

Table 1

General characteristic of the study and control groups

Comparable parameters	Group 1 (n=12) IRI-guided PDT	Group 2 (n=8) PDT without IRI-control	p
Gender* (male/female)	5/7	3/5	0.663/0.666
Age* (years) Me [25; 75]	52 [44; 62]	53 [51; 60]	Ur
Tumor grade (Grade II/Grade IV/MTS)	0/12/0	1/6/1	0.368/0.779/Ur
Tumor localization in hemispheres* (right/left)	5/7	4/4	0.43/0.86
Tumor dissemination* (one lobe/two or more lobes)	5/7	4/4	0.43/0.86
PDT duration** (min)	10 [6; 15]	11 [8; 18]	0.67
Karnofsky scale before surgery** (scores)	60 [60; 70]	60 [60; 70]	0.75

Note. Ur: unreliable; MTS: metastases; * Fisher's exact test, and χ^2 test with Yates' correction; ** Mann–Whitney U-test.

tissues. In contrast to a laser technique — interstitial laser thermal destruction — used in the therapy of brain tumors, a thermal effect in PDT is known to have no damaging action. However, if in general oncology this side effect can be paid no particular attention, in neurosurgery even relatively slight increase of brain tissue temperature, especially in functionally or life-critical areas, can lead to complications [13]. Previously, we showed [14] that PDT contributes to the perifocal edema increase in a postoperative period, and can result in an increasing number of neurological disturbances. But up to now the search for methods aimed at alleviating PDT-induced peritumoral edema is essential [15].

The aim of the investigation was to assess the role of infrared imaging for brain tissue heating when exposed to laser radiation in photodynamic therapy of removed tumor bed brain, and its effect on postoperative edema.

Materials and Methods. PDT in the treatment of brain tumors has been applied in Nizhny Novgorod Research Institute of Traumatology and Orthopedics since August 2011 by the decision of the Ethics Committee dated 24.10.2011 and Academic Council of the Institute dated 25.10.2011.

The study was carried out in accordance with the declaration of Helsinki (adopted in June, 1964 (Helsinki, Finland) and revised in October, 2000 (Edinburg, Scotland)). All patients gave their informed consent.

We studied the treatment results of 20 patients with malignant brain tumors with intra-operative PDT. The patients were divided into two groups: group 1 patients (n=12) had intra-operative infrared imaging (IRI)-guided PDT, and group 2 control patients (n=8) had no IRI control. In group 1 all 12 patients had glial tumors; in group 2 only 7 patients had such tumors, and 1 patients had multiple metastases. On admission, all patients underwent standard neurological and laboratory examinations, and brain computed tomography, their quality of life being assessed according to Karnofsky scale.

The comparison of the groups by a number of parameters obtained on admission by the patients' examination by means of normal distribution analysis showed both groups to be similar in gender, tumor process localization and dissemination, the quality of life (Table 1).

As a photosensitizer in PDT we used Fotoditazin at a dose of 0.8–1.0 mg/kg. Radiation was produced by a semiconductor laser with wavelength 661 nm, on average 4–6 h after administration. In superficial tumors we used the light guide's edge, the radiation power being 2.0 W, in deep tumors we used a light-guide with additional attachments, radiation power being 2.5 W. A thermal effect of PDT was assessed continuously using an IRI-camera Thermo Tracer TH-9100 (NEC Avio Infrared Technologies, Ltd., Japan) operating in a spectral range 8–14 μm, the sensitivity being 0.025–0.03°C with error ±1%, and infrared sensor resolution was 320×240 pixels. The camera was stationary placed so to have the maximal viewing of the tumor bed, and not to disturb an operating team and maintain sterile conditions (Figure 1).

A restraining value of limiting high temperature of brain tissues was considered 37.63°C [13]. The camera continuously monitoring the wound surface signaled to warn if the temperature in any part of the area under radiation exceeded 37.6°C. In this case a brain wound was filled by a sterile saline solution at 24–26°C to cool followed by aspiration using a suction device. When meticulous hemostasis is achieved, laser radiation with wavelength 661 nm penetrates through a physiological solution, therefore, PDT and IRI-control procedures were not stopped on cooling.

The estimated measurements of the perifocal edema during the pre- and postoperative periods were compared in 12 patients, who had undergone IRI-guided PDT, and in 8 patients after PDT without IRI control. The measurements of masses were assessed by CT findings performed on Toshiba Aquilion 32 (Toshiba,

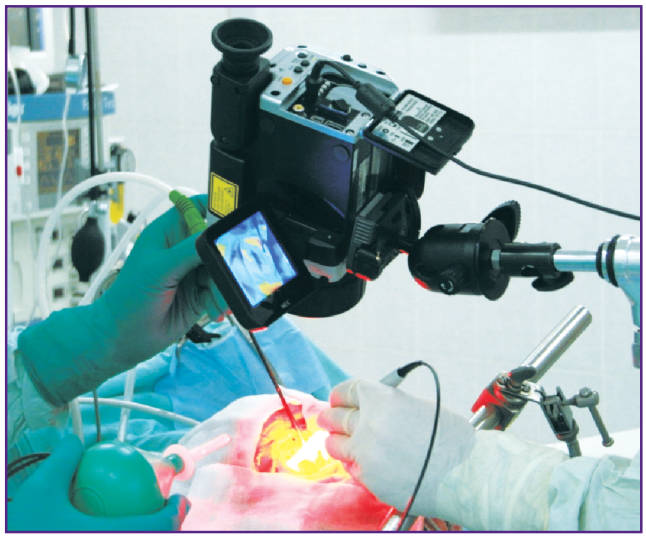

Figure 1. Intraoperative thermal control of photodynamic therapy

Japan) during the pre-operative period and on the first postoperative day. To compare a tumor size in axial and coronal views, as well as a tumor and perifocal edema in similar sections in pre- and postoperative periods, we used a standard software environment Vitrea for a computed tomography scanner Toshiba Aquilion 32, as well as Onis 2.5 free edition (www.onis-viewer.com). Then we compared the pre- and postoperative sizes of perifocal edema in both groups.

All patients before and after PDT underwent histological examination of identical areas of the tumor bed wall formed after tumor removal (perifocal area). The study was carried out after the preliminary material fixation in neutral formalin solution. Standard histological investigation was performed on Excelsior ES (Thermo Scientific, USA) followed by paraffin block formation using HistoStar (Thermo Scientific, USA). The series sections, 4–6 μm thick, were made on Microm HM 325 (Thermo Scientific, USA). The sections were hematoxylin and eosin stained and stored. Morphometric complex Leica DMR (Leica Microsystems, Germany) was applied for microscopy and photographic documentation. Semi-thin sections, 1 μm thick, were prepared from polymerized EPON blocks using an ultra-microtome PowerTome PC (RMC Products, USA). Tissue samples were preliminary fixed according to a standard technique in 2.5% glutaric dialdehyde on a phosphate buffer followed by post-fixation by osmium tetroxide, evaluation and embedding in epoxide resin. After resin removal, in accordance with the recommendations by Humphrey et al. (1974) semi-thin sections were subject to polychrome staged staining by methylene blue, azure II, basic fuchsin to contrast cytological details.

Results and Discussion. According to our findings, mean temperature of the tumor bed after tumor removal was 32.16±2.67°C, and that of the perifocal area of the brain wound (the area bordering the wound, its margin being 1 cm away from the edge) was 32.09±1.85°C, and the temperature of the far away cortex was 34.59±1.69°C (Figure 2). We studied the integral values of temperatures of each of the three areas.

In the control group IRI-measurements before and within 5 min before PDT termination in these three areas inside an open segment enabled to reveal the temperature changes in the brain wound, in its perifocal area and in the far away cortex (Figure 3). Since due to the variety of clinical contexts we could not obtain reliable data for the existing sampling and assessed just the tendencies of changes in response to PDT.

It is evident that the PDT effect on local cerebral blood flow in relatively intact cortex being at over 1-cm-distance of the incisional wound is insignificant. The 3–5-minute delay of temperature increase in a brain wound is explained by the absence of natural convection due to a cuvette effect in a deep cavity after uncontrolled heating induced by radiation. From our point of view, significant (over 1°C) and stable temperature decrease in the perifocal area of the brain wound can appear

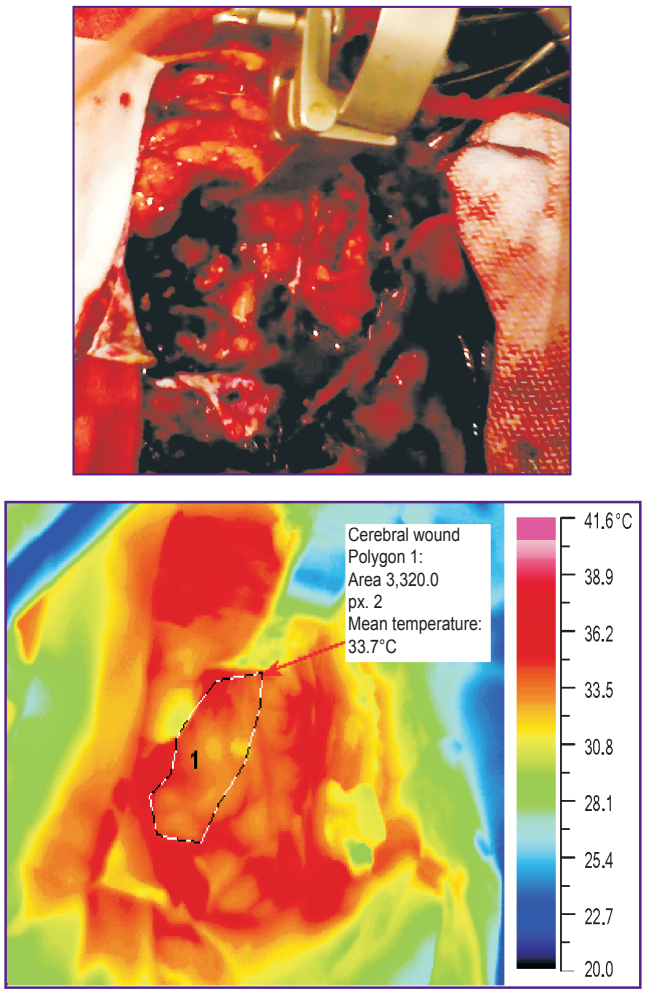

Figure 2. An example of temperature distribution of the brain wound surface after tumor removal

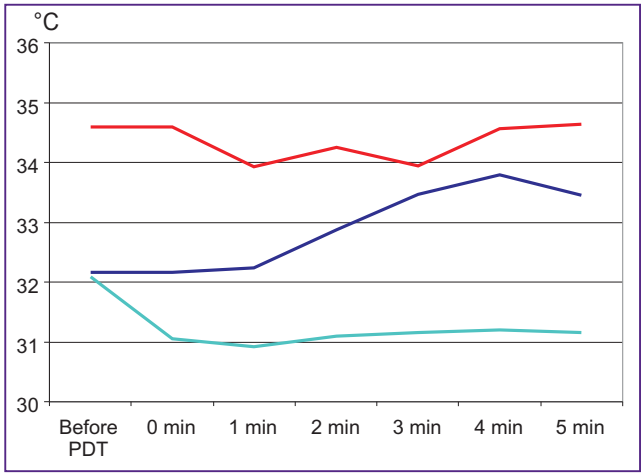

Figure 3. Temperature dynamics in the brain wound (*blue curve*), the perifocal area (*light blue curve*) and the far away cortex (*red curve*) before and within 5 min after photodynamic therapy in controls (n=8)

more critical: our previous studies [16] showed that after surgical procedures this cortical zone should be heated and its cooling is an unfavorable prognostic sign. This fact appeared to be a supplementary ground for developing a technique to control maximum allowable heating of cerebral tissues.

Table 2 presents the perifocal edema sizes and dynamics in axial and coronal sections in both groups.

According to the study of axial and coronal sections, in the study group, the perifocal edema on day 1 after surgery decreased and was 50.4 [16.4; 79.3] and 88.5 [30.3; 110.6]% of the preoperative one, respectively. The postoperative edema in the controls without IRI-control was 227.9 [92.4; 303.8] and 154.7 [84.5; 150.3]% of the initial one. In addition, the dynamics of the perifocal edema on an axial section appeared to be significant, p=0.004 (Figure 4).

Performed calculations showed that postoperative perifocal edema in the study group decreased by 20–

Table 2

Perifocal edema sizes and dynamics in photodynamic therapy with and without infrared imaging control

Comparable parameters (by Mann–Whitney U-test)	Group 1 (n=12) IRI-guided PDT Me [Q1; Q2]	Group 2 (n=8) PDT without IRI control Me [Q1; Q2]	Significance point (p)
Edema size in axial section:			
preoperative (mm^2)	3,531 [2,025; 3,880]	2,204 [266; 3,642]	0.14
postoperative (mm^2)	1,555 [456; 2,980]	4,535 [1,072; 6,402]	0.057
Edema size in coronal section:			
preoperative (mm^2)	3,123 [1,161; 4,683]	2,307 [942; 4,050]	0.65
postoperative (mm^2)	1,754 [496; 3,471]	3,285 [1,200; 5,945]	0.17
Ratio of postoperative perifocal edema to pre-operative one:			
on axial section (%)	50.4 [16.4; 79.3]	227.9 [92.4; 303.8]	0.004
on coronal section (%)	88.5 [30.3; 110.6]	154.7 [84.5; 150.3]	0.11

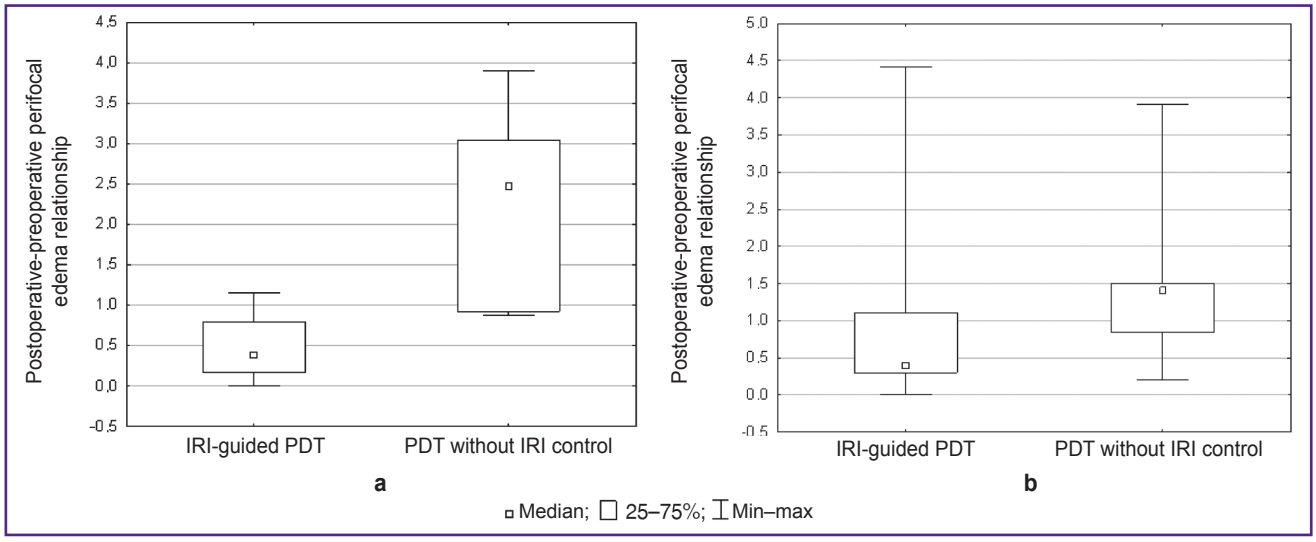

Figure 4. The ratio of postoperative perifocal edema to preoperative edema on an axial (a) and coronal sections (b)

50%, while in the control group it increased by 50–230%.

The state of group 1 patients according to Karnofsky scale on postoperative day 5–6 was 80.5 [70; 90] scores, in the second group it was 70 [60; 80] scores, and on discharge their state was 80 [70; 90] and 80 [60; 90], respectively.

Histological examination of the perifocal area before PDT in both groups revealed that on semi-thin sections of preparations there was rather close spacing of cell elements with full-blood vessels (Figure 5 (a)). After PDT there was marked perivascular and pericellular edema of cellular tissue with rather separately cell elements (Figure 5 (b)).

Thus, histological examination of identical areas of brain tumor bed wall before and after PDT proved the formation of brain tissue edema in a perifocal area developed immediately after PDT.

The significance of temperature control during PDT is due to the fact that if the radiation exposed tumor bed formed after the tumor removal, and the end piece of the light guide is held in the same point just for several seconds, it can result in local temperature rise of the exposed tissues up to 38°C (Figure 6).

The analysis of immediate treatment results of patients with malignant brain tumors at thermal control during PDT suggests the decrease of a postoperative edema size compared to the preoperative one. In case of incomplete tumor removal, its remaining parts, intracerebral hematomas in the tumor bed on their own are the causes of edema persistence during the postoperative period. In the study group there were 10 cases with complete tumor dissections, 1 case with subtotal oncotomy, and 1 case with partially removed tumor. Two patients were found to have small postoperative hematomas in the tumor bed requiring no operative intervention. However, all patients in the group were found to have decreased edema area in the postoperative period. In the control group significant increase of edema was primarily due to a thermal effect since 7 patients had their tumors completely removed, 1 patients had partial tumor removal; and in one female patient on the first postoperative day acute cerebrovascular accident occurred with intracerebral hematoma formed in the wound area followed by surgical resection of the hematoma. Mean PDT time in both groups was nearly the same (See Table 1). In group 2 three patients had no postoperative cysts in the surgical area, which frequently develop after tumor removal, and the tumor bed collapsed against the postoperative edema.

The life quality of the patients according Karnofsky scale estimated on discharge appeared to be the same in both groups.

Postoperatively, depending on edema intensity according to CT findings, the patients were administered a corresponding dose of dexamethasone: from 4 to 24 mg on the first day with gradual step-down in dosage. The necessity for a longer anti-edemic therapy to reduce the postoperative edema resulted in the increase in the average hospital stay: from 16.0 [12; 21.5] days in the study group to 20.8 [14; 28] days in the control group. Edema developing after PDT was resistant to dexamethasone therapy, and regressed on 14–21 postoperative day.

There are the following examples.

Example 1. Patient G., 64 years old, operated on 07.02.2013 for the right postfrontal parietotemporal glioblastoma; after tumor resection he underwent PDT without IRI control. The radiation power was 2 W, the light dose was 180 J, the radiation time being 15 min. Figure 7 represents pre- and postoperative computed tomograms of the patient.

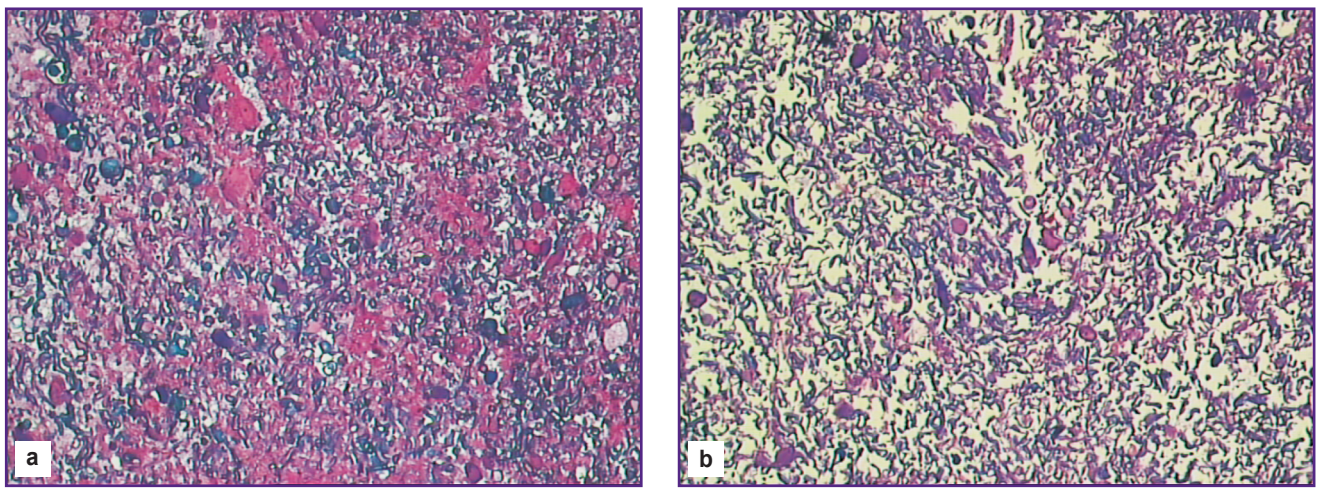

Figure 5. Perifocal tumor area: (a) before photodynamic therapy; (b) after PDT; ×400, staged staining by methylene blue, azure II, main fuchsin

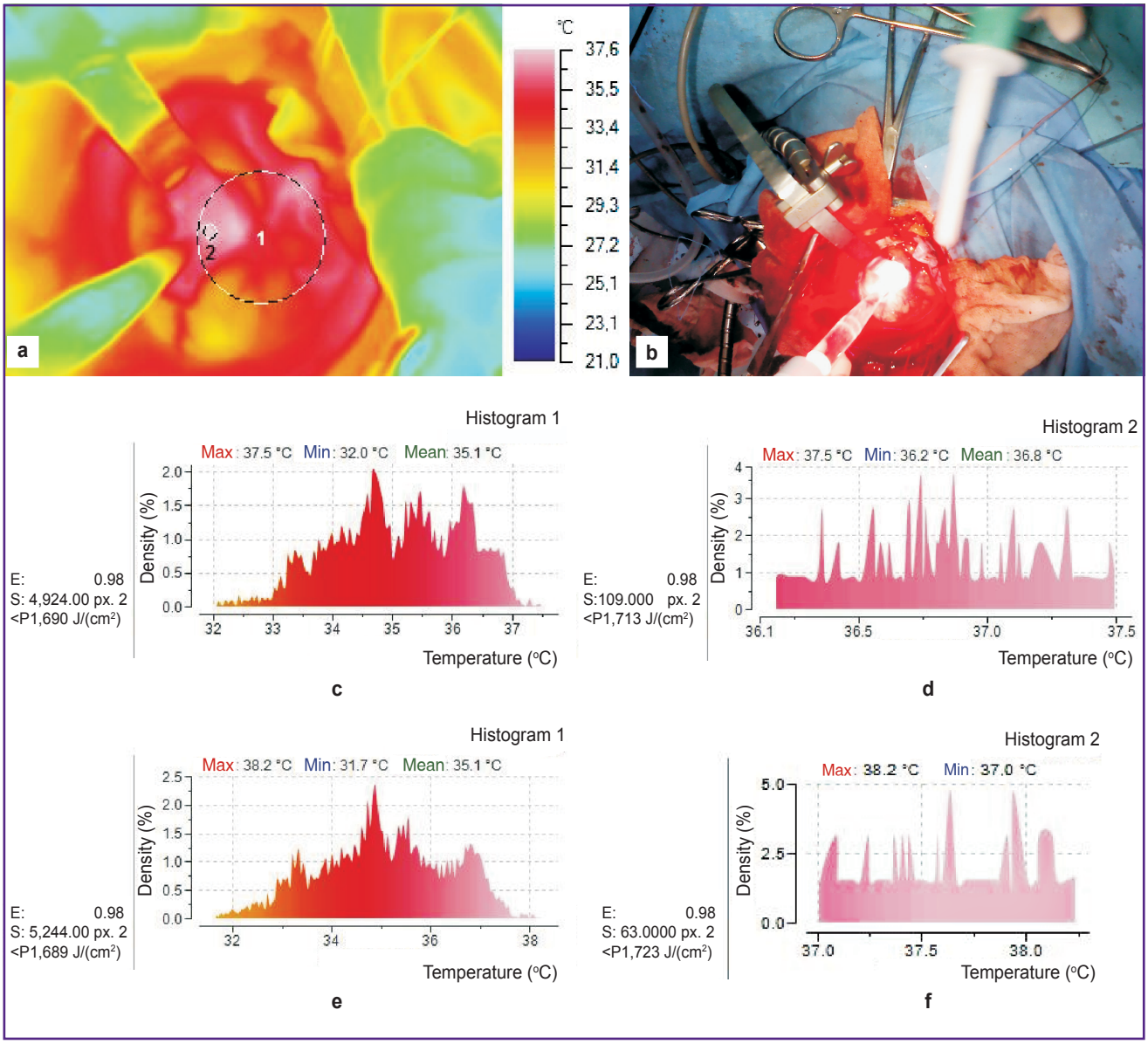

Figure 6. The rise of maximum allowable temperature in photodynamic therapy: (a) a thermal map of the cerebral wound during radiation; (b) an intra-operative photo of PDT process; (c), (e) histograms of temperature distribution in area 1 (the brain wound bed in general); (d), (f) histograms of temperature distribution in area 2 (below the end piece) with maximal temperature **37.5°C** ((c), (d) recording time **15.34.00**) and **38.2°C** ((e), (f) recording time **15.34.04**)

Example 2. Female patient F., 56 years old, operated on 04.01.2014 for postfrontal parietotemporal glioblastoma. After the tumor resection she underwent IRI-guided PDT. The radiation power was 2 W, the light dose was 180 J, the radiation time being 15 min. Figure 8 represents pre- and postoperative computed tomograms of the female patient.

The examples provided clearly demonstrate the efficiency of IRI-guided PDT. Figure 7 shows the edema growth in axial and coronal views in the operative zone at PDT without IRI control on day 7 after surgery compared to the pre-operative period. In Figure 8 the edema on day 6 after the operation in the operative zone at IRI-guided PDT is less marked compared to that in the preoperative period.

Conclusion. Photodynamic therapy of cerebral tumor process is accompanied by the temperature rise of the exposed tissues. It is one of the causes of an increasing perifocal edema in an early postoperative period. The use of infrared control at photodynamic therapy and the irrigation of a tumor bed by cooled sterile saline enable to avoid overheating of tissues and edema growth that makes it possible to reduce a patient's hospital stay.

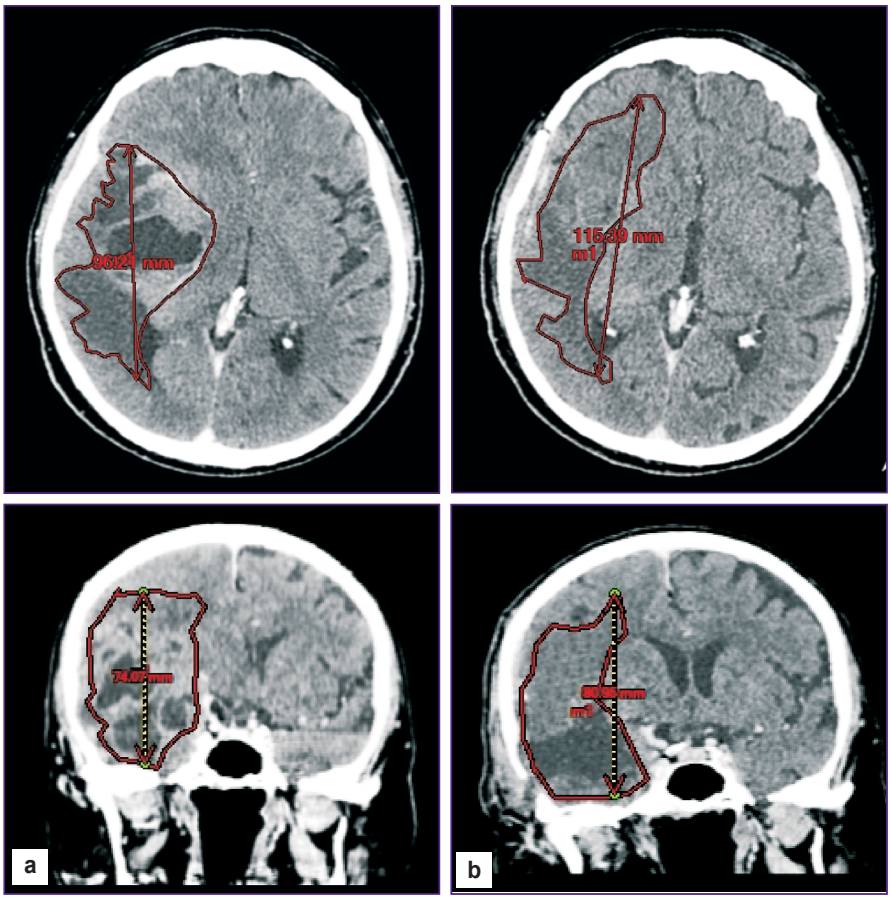

Figure 7. Computed tomograms of a 64-year-old patient G., who underwent PDT without IRI control: (a) the preoperative tomogram dated 05.02.13; (b) the postoperative tomogram dated 14.02.13; the red line shows tumor zones and cysts before surgery (a) and postoperative cysts and edema after the operation (b); the postoperative tomograms show no subarachnoid spaces in the right postfrontal parietotemporal region

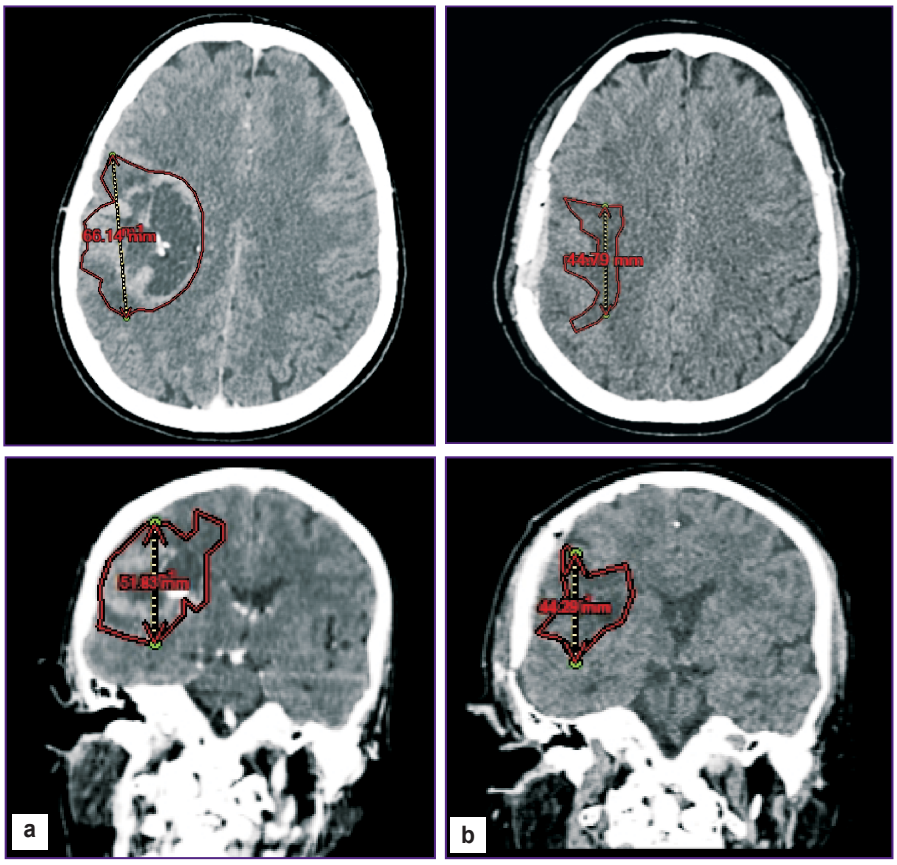

Figure 8. Computed tomograms of a 56-year-old female patient F., who underwent IRI-guided PDT: (a) preoperative tomograms dated 02.01.14; (b) postoperative tomograms dated 10.01.14; the red line indicated the tumor zones and cysts before the surgery (a) and postoperative cysts and edema (b); the postoperative tomograms show smoothed subarachnoid spaces in the right postfrontal parietotemporal region

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