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THE RESULTS OF THE STUDY OF HUMAN ANOMALOUS THERMAL FIELDS UNDER IRRADIATION

The results of thermal imaging study of thermal fields on the skin surface of cancer patients treated with radiotherapy have been presented. Quantitative and statistical approach to the analysis of thermal images has been described. The results of thermal survey of patients before the start of irradiation have showed that thermal imaging diagnostics of the majority of internal tumors is limited or even impossible. However, the obtained correlation coefficients R = 0.76÷0.81 between the thermal parameters and the clinical side toxic reaction indicators, as well as the resulting «good quality» parameter of prognosis method have proved the possibility of using the thermal imaging method for monitoring and prediction of side toxic reactions of radiation therapy. The necessity of increasing the statistical power of the analyzed samples has been noted.

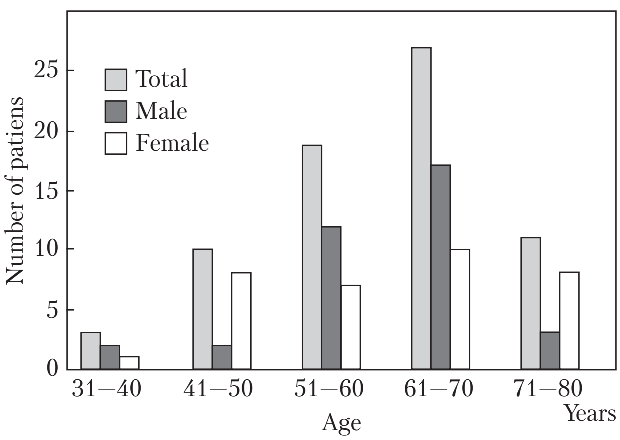
Keywords: thermal imaging, tumor, radiotherapy, and side toxic reactions.

Infrared medical thermography [1] is based on contactless remote record of intrinsic radiation of human skin that reflects various physiological and biochemical processes in the body tissues. In Ukraine, thermography in medicine has been used since the beginning of the 1980s, the initiators of its introduction are Academicians A.F. Vozianov and L.G. Rosenfeld. However, the lack of domestic production of thermographs, as well as widespread use of ultrasound, X-ray, and magnetic resonance tomography have led to a decrease in the role of clinical thermodiagnostics. Recently, due to emergence of a new class of uncooled matrix thermographs, interest in this method for surveying patients has been resumed.

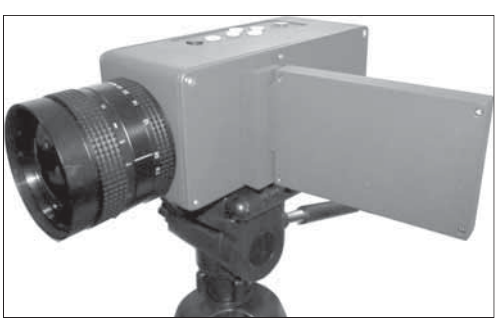
The method of medical thermography has two significant advantages over the conventional clinical imaging methods. Firstly, it is a method of functional analysis, which enables obtaining important additional information that is inaccessible to MRI, X-ray and ultrasound surveys, which give information, basically, about the anatomical structures of the body. Secondly, this method is absolutely non-invasive, which enables to thermograph the patient as many times as required without any harm to his/her health. Despite this, for the time being, the method is extremely rarely used in clinical medicine, mainly because of ambiguous interpretation of thermal image (thermogram) as a result of insufficient knowledge of the pathophysiological fundamentals of human skin thermal fields.

Thermographic studies have been carried out within the framework of R&D innovation project of the NAS of Ukraine *Development of a Thermographic Complex for Medical Applications and Thermal Imaging Techniques for Quantitative Analysis* *of the Dynamics of Anomalous Human Thermal Fields*. The research continues the studies conducted by the authors in collaboration with American and Ukrainian oncologists [2, 3]. The idea of such research cycle is based on suggestion about correlation between the features of the dynamics of anomalous thermal fields on the skin of cancer patients and the changes in the clinical parameters of the tumor, as well as the level of body's toxic adverse reactions on irradiation. As of today, in the world there is neither method nor criterion for estimating individual «tolerance» to irradiation. The identification of this criterion is an important stage for predicting the severity of possible side effects in order to select an individual exposure regime and to take necessary preventive measures. Therefore, the main purpose of the whole research cycle is the creation and implementation of thermal imaging technique in the clinical oncology to ensure quantitative control of local adverse reactions to irradiation and early prediction of their individual level for each patient [2, 3]. Achieving this goal is impossible unless a sufficient amount of experimental data supporting the proposed idea is accumulated.

This paper gives a brief description of quantitative and statistical approach to the analysis of thermal images and presents some of the results obtained. More detailed results of these studies have been published in special medical publications [3—5].



a



b

Fig. 1. Age of patients involved in the study (*a*) and appearance of thermal field analyzer (*b*)

MATERIALS AND METHODS OF RESEARCH

The dynamics of anomalous thermal fields on the skin of patients with oncological diseases treated with radiation therapy (RT) have been studied by non-invasive passive local-projection method of infrared thermography [6]. A group of 70 adult patients with malignant tumors of various types, stages, and locations, including 25 patients with tumors of ENT organs (larynx, tonsils, tongue, vocal cords, etc.), 10 patients with cutaneous tumors, 15 patients with breast neoplasms, and 20 patients with neoplasms of other organs (gastrointestinal tract, lungs, bones) has been surveyed (Fig. 1, *a*). The patients were irradiated using gamma-therapeutic devices *ROCUS-M* and *Theratron Elite-80*. The standard patterns and radiation doses were used depending on specific location of the tumor. At the first stage of radiation therapy for the majority of internal and cutaneous tumors, the single radiation dose (SRD) and the total focal radiation dose (TRD) were: SRD $\approx$ (2÷3) Gy, TRD $\approx$ 40 Gy. For breast cancer: SRD $\approx$ (2÷3) Gy; TRD $\approx$ (40÷60) Gy on the primary site and TRD $\approx$ 40 Gy on lymph efflux paths (axillary and subclavian lymph nodes). Sites having various area (for instance, S $\approx 8\times12$ cm^2 on both neck sides in the case of laryngeal cancer, S $\approx 5\times5$ cm^2 in the case of small basalioma, etc) were irradiated.

The patients were surveyed in a specially equipped room with all climatic requirements and rules

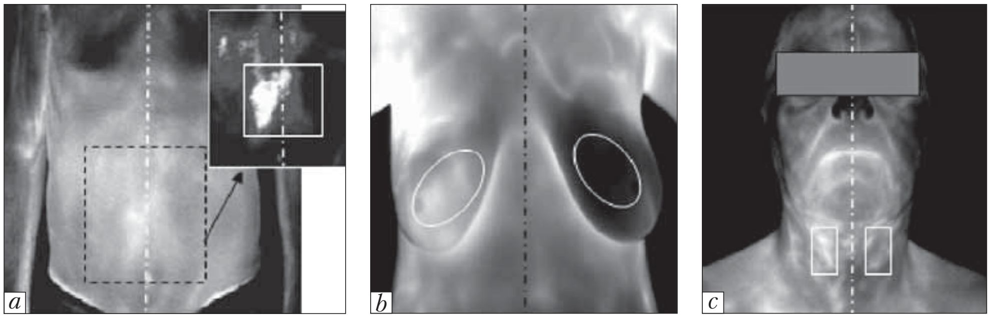


Fig. 2. Examples of thermal asymmetry in tumor projection: *a* — pancreas cancer (on the inset: a fragment of thermogram for other temperature range; (ΔT = 0.6 °C with a site of interest 5×7 cm^2); *b* — right breast cancer (ΔT = 3.4 °C); *c* — right larynx cancer (ΔT = 0.9 °C)

of patient preparation met. Thermography was carried out by analyzer of thermal fields designed at Verkin Institute for Low Temperature Physics and Engineering of the NAS of Ukraine on the basis of uncooled matrix (384 × 288) of microbolometric receivers [6]. The «open architecture» and modular design of the analyzer hardware and software components enable to adapt the device to clinical use as much as possible.

Each patient was surveyed before RT (basic thermographic session) and before each subsequent week of treatment with radiation. The standard course at the first stage was 4 weeks (5 sessions per week), so each patient engaged was thermographed at regular intervals, at least, 5 times (patients undergoing two RT stages are thermographed up to 10 times). A relative temperature scale (with respect to the reference temperature) was used to quantify the changes in the intensity of thermal fields, with the site of the reference temperature chosen individually depending on the tumor location and remaining unchanged for the individual patient during the subsequent monitoring. The possibility of diagnosing neoplasms by thermographic method was determined before the start of RT by the criterion of thermal symmetry distortion [6], according to which the site of reference temperature is symmetric, contralateral, and identical in shape and size to the site of interest.

The thermal data and clinical indices of a group of 19 patients with head and neck tumors who have undergone a full course of radiation therapy are used for statistical analysis. Methods of statistical analysis used in domestic medicine have been used.

THERMAL DIAGNOSTICS OF MALIGNANT NEOPLASMS

In line with the main purpose of the research and the methodology used for quantitative analysis, the thermal data of baseline session underlay quantitative analysis of further changes in anomalous thermal fields during radiation therapy. The results of basic session also made it possible to assess the possibilities and limitations of the thermal method for the diagnosis of malignant tumors of various types, stages, and localizations.

Thermographic survey was carried out for the group of patients with established diagnosis. Therefore, hereafter thermal diagnostics means detection by thermographic method of anomalous hyperthermic sites before RT treatment (assumed thermal imprints of tumor on skin) using selected quantitative criterion of thermal symmetry distortion $\Delta T \geq 0{,}5$ °C, where ΔT is difference of average temperatures of the site having an area of, at least, 10 cm2 in the projection of tumor to the nearest skin area and the symmetrical sound site of the same size and shape.

Fig. 2 shows examples of thermograms of patients with detected anomalous sites in tumor projections. The sites for quantitative estimate of thermal asymmetry (hereinafter, «the site of interest») are marked with white rectangles or ovals.

Table 1 features a ratio of the number of patients with detected anomalous hyperthermic sites to the total amount of patients with tumors of similar localization. The Table data have confirmed generally accepted fact [7] that breast cancer can be detected by thermographic method based the thermal asymmetry criterion, as for all patients, hyperthermic sites of large area with significant thermal asymmetry were found. A significant thermal asymmetry over a large area was reported for lymphoma projections as well [3]. The detection of cutaneous neoplasms is out of interest since they are visible. However, a low level of detection of hyperthermic sites in projections of tumors with other localizations has testified to limited or impossible thermal diagnostics of majority of internal neoplasms.

Average temperatures of anomalous thermal field before RT in site of interest having the same shape and size have been compared for five patient pairs with the same location and nosological shape of the tumors but with different dispersion (extent) (x index in the tumor classifier $T_xN_yM_z$). No correlation between tumor size and skin thermal field parameters in tumor projections has been detected (Fig. 3).

MONITORING AND PREDICTION OF LOCAL REACTIONS ON RADIATION

According to the idea of the whole cycle of studies [2], the parameters of changes in the intensity of thermal fields in certain areas of the skin surface can be a quantitative criterion for assessing the level of local adverse reactions, namely, radial oral mucositis (OM, inflammation of the oral mucosa) and a prediction criterion of patient's individual RT tolerance at the beginning of the treatment. To check this assumption, quantitative and statistical analysis of correlation between the dynamics of clinical mucositis index and changes in the intensity of anomalous thermal fields in the site of interest has been made for a selected group of 19 patients with head and neck tumors. The average temperature of the eyelid segments near the nose bridge was used as reference temperature for each patient, in each thermal imaging session [9], with a non-irradiated area of of 5×2 cm^2 of the outer surface of the lower lip chosen as site of interest.

Fig. 4, *a* shows a patient's frontal thermogram with the site of interest marked with a black rectangle; the threshold area is marked with white oval. In Fig. 4, b there is an example of changes in thermal and clinical parameters for one of the patients during the RT treatment course. Curve *1* shows change in reduced temperature ΔT, where

Table 1

Assessment of Detection of Thermal Imprints in Projection of Tumors of Various Localization

Location of tumor	Patients in group	Patients with detected thermal asymmetry, $\Delta T \geq 0{,}5$ °C, $S \geq 10$ cm^2	Group average thermal asymmetry in tumor projection, °C
Larynx, oropharynx, vocal cords	12	5	0.65
Breast	7	7	1.85
Tongue, tonsils, mucous membrane of the mouth	8	2	0.7
Skin (neoplasms are observed visually)	13	13	—
Organs of digestion	9	2	0.7
Lungs	2	2	0.7
Lymphomas of various localization	4	3	2.8
Affected lymph nodes	4	4	1.0
Bone tissues	1	1	2.4

$\Delta T = \Delta T_i - \Delta T_0$ is difference between the average relative temperature in the site of interest at the i-th thermal imaging session and the corresponding temperature at the basic session. Curve *2* shows change in the clinical indicator of mucositis determined by the physician based on visual survey before each RT session. Curve *3* describes change in the deterioration of quality of life (QOL) assessed based on patients' answers to questions from a specially developed questionnaire.

Correlation between the reduced temperature ΔT and the clinical data (OM and QOL) in the studied group of patients was assessed for each thermal imaging session (Table 2).

Moreover, when analyzing the thermal and clinical data, a correlation between the reduced temperature in the site of interest for the first thermographic session and the maximum level of mucositis that subsequently developed in each patient of the group was clearly observed.

To verify the presence and nature of the observed correlation, the Spearman correlation coefficient p was calculated and its significance was estimated by comparison with critical point T_{cr} [10]. The obtained values ($p = 0.76$, $T_{cr} = 0.33$, $T_{cr} < p$) have confirmed a direct and strong correlation between the given thermal parameters of the first thermographic session and the maximum

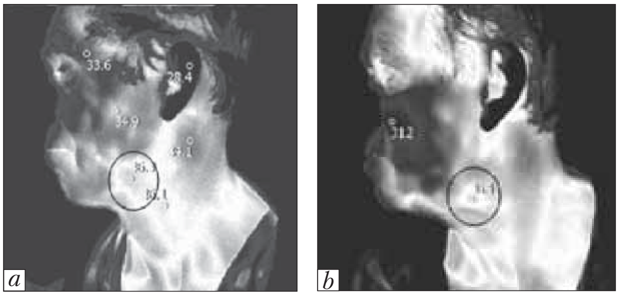


Fig. 3. Thermograms of two patients of approximately same age and body constitution with cancer of mucous membrane of the left mouth bottom before treatment, in uniform temperature scale: *a* — $T_2N_1M_0$ (ΔT = 1.0 °C), *b* — $T_3N_2M_0$ (ΔT = 0.7 °C). The same sites of interest are marked with black ovals

OM level. Proceeding from the above, it is supposed possible to predict the future maximum level of mucositis based on the results of the first thermographic session. So, at $(\Delta T)_1 \geq 0.9$ °C, reaching of maximum level of mucositis OM > 3.can be predicted.

The following parameters were calculated in order to assess informativity and resolution of proposed forecast method using statistical criteria applicable in medical science [11]:

✦ Sensitivity of method = 0.8 (the share of patients with $\Delta T \geq 0.9$ °C at the first thermal imaging session in the total number of patients

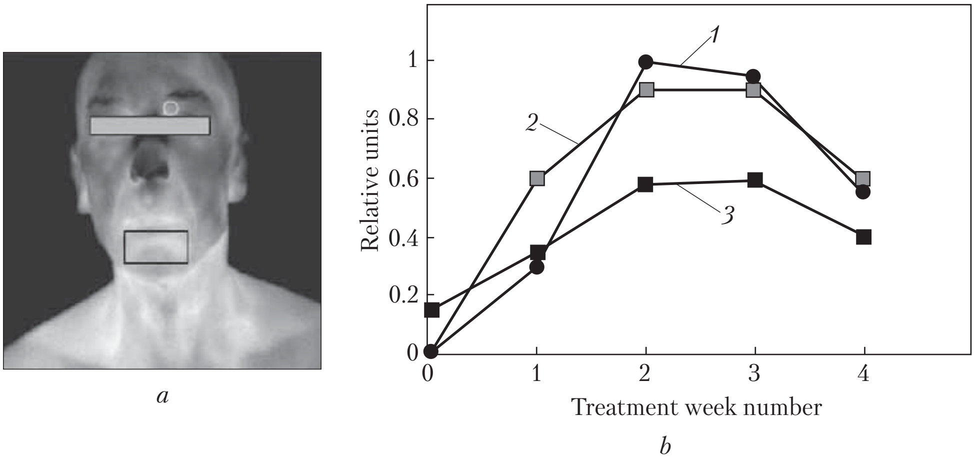


Fig. 4. Dynamics of thermal and clinical indicators of patient in the course of RT treatment: *a* — patient's frontal thermogram with the site of interest marked with a black rectangle and the threshold area marked with white oval; *b* — changes in reduced temperature ΔT of the site of interest (*1*), change in OM factor (*2*), deterioration of quality of life (*3*)

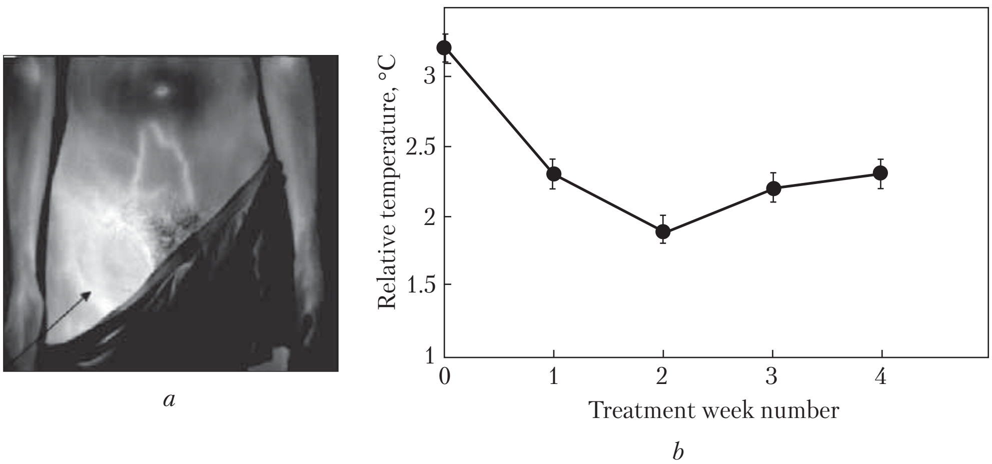


Fig. 5. Dynamics of anomalous thermal field in the projection of right groin lymphoma: *a* — thermogram of a patient with groin lymphoma (indicated by an arrow) before the start of RT; *b* — change in the relative average temperature in 20×20 cm^2 site of interest (in lymphoma projection)

with high level of toxic reactions, OM > 3 after RT treatment);

- Specificity of method = 0.785 (the share of patients with $\Delta T < 0.9$ °C at the first thermal imaging session in the total number of patients without high level of toxic reactions, OM ≤ 3 after RT treatment);
- Accuracy of method = 0.789 (the share of correct method-based forecasts for the whole group of patients tested).

Based on the sensitivity and specificity data, a Receiver Operating Characteristic (ROC) curve [12] is built. It demonstrates how the number of correctly predicted (actual) high-level toxic reactions depends on the number of incorrectly predicted (absent) high-level toxic reactions. Area under ROC curve (AUC) is equal to 0.79, which means «good quality» of the proposed method for predicting the individual level of development of radial oral mucositis.

Table 2

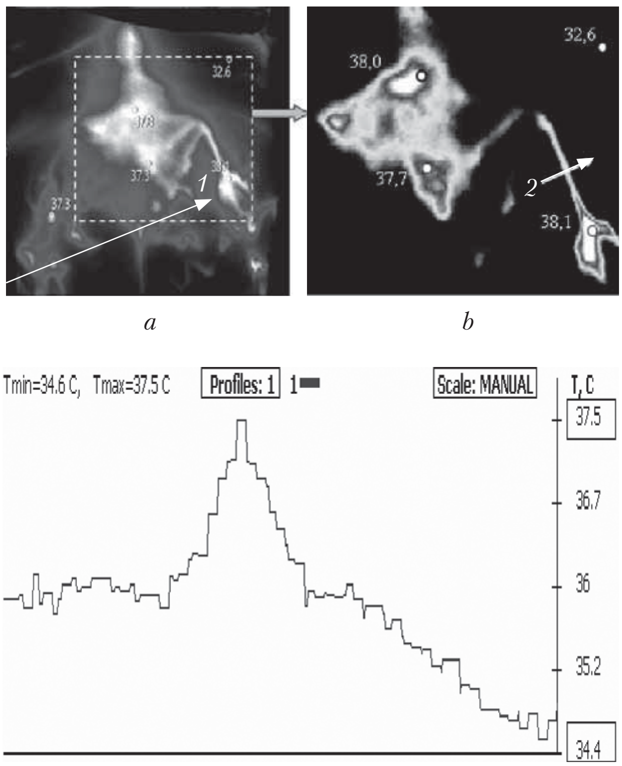
Correlation between Thermal and Clinical Indicators for the Test Group (*n* = 19 patients)

Correlation	Session			
	1	2	3	4
R (ΔT : OM)$_{1...19}$	0.775	0.756	0.787	0.807
R (ΔT : QOL)$_{1...19}$	0.793	0.761	0.806	0.827

The obtained results indicate a high correlation between the relative average temperature in the selected site of interest and the clinical data, and the possibility of using the method for predicting the individual level of development of mucositis. It should be noted that the results were obtained on samples with insufficient statistical power (19 patients), and additional studies in this direction are needed.

DYNAMICS OF THERMAL IMPRINTS OF LYMPHOMAS AND LYMPH NODES

In previous studies, no decrease in temperature of thermal imprint of the tumor (decrease in intrinsic temperature of the tumor) due to RT was reported, since the thermal imprint area always coincided with the irradiated area, which led to a significant increase in temperature because of development of radiation dermatitis. At this stage of the study, an expected decrease in temperature of the thermal imprint at the beginning of RT (5—10 sessions) has been observed in the patients with lymphomas and affected lymph nodes. With further irradiation, the temperature in the site of in-



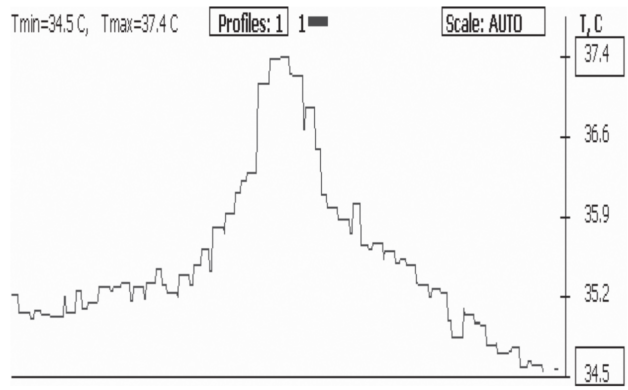


Fig. 6. Thermal strands in patient with metastasis of the right hip and ilium bone and with undiagnosed primary focus: *a* — thermogram of pelvic before RT (assumed thermal imprint of metastasis is indicated by arrow), *b* — enlarged fragment of thermogram with thermal cross section indicated by arrow, *c* — thermal cross section of strand before RT, *d* — the same thermal cross section after 10 RT sessions

terest increases because of radiation reactions. Fig. 5 shows an example of such correlation, where a thermogram of a patient with groin lymphoma (indicated by an arrow) before the start of RT (*a*) and a diagram of change in the relative average temperature in the site of interest (*b*) are presented. With such tumor localization, the scale of relative temperature is based on the criterion of thermal symmetry distortion, i.e. difference between the average temperature of 20×20 cm^2 site of interest in the projection of lymphoma coinciding with the irradiated area and that of the symmetric sound non-irradiated area is estimated. In this case, a significant decrease in the relative temperature (≈ 2.5 °C) during the first 2 weeks of RT (10 sessions) is reported, which can be explained by a decrease in the intrinsic temperature of lymphoma and in its volume. Later, an insignificant increase (≈ 0.5 °C) is observed, presumably, because of development of radiation dermatitis. A significant decrease in temperature of thermal imprint has been confirmed by medical conclusion on regression of the tumor size, from 18 cm to 10 cm in diameter, due to irradiation.

Having compared the temperature dynamics in the sites of interest, with changes in the clinical parameters of radiation reactions for the patients [4] taken into consideration, one can assume the presence of simultaneous processes:

1) a decrease in skin temperature in the projection of lymphomas and affected lymph nodes as a result of tumor regression due to RT;

2) an increase in skin temperature because of development of local adverse reactions to radiation.

No decrease in temperature of thermal impressions of other forms of tumors has been recorded as a result of increase in temperature caused by development of radiation reactions.

OBSERVATION OF THERMAL STRANDS

During the study of thermal fields on the skin of patients with cancer, a significant amount of anomalous thermal strands has been observed in the area adjacent to the tumor projection (Fig. 5, *a*). Such thermal strands are thermal impressions of «overheated» vascular pathways of the lymphatic or circulatory type. Detection of thermal strands and their correct interpretation can be important in the cases of undiagnosed primary foci and precise knowledge of the lymphatic drainage pathway enable targeted search for lymph nodes with metastatic lesions in patients with detected malignant tumors [5]. In the course of study, the researchers tried to establish a correlation between the presence of thermal strands on the surface of the patient's skin and the characteristics of malignant neoplasm and to monitor the temperature dynamics of strands during RT.

Fig. 6 shows a thermogram of pelvic of a patient with diagnosis based on results of MRI and radiography surveys, before the start of RT: a metastasis of the right hip and ilium bone with undiagnosed primary focus. On the thermogram, there are anomalous hyperthermic strands whose temperature is few degrees higher than that of the adjacent areas of the skin. Also, one can see that the hyperthermic area in the metastasis projection (T_{max} = 38.1 °C) is linked by hyperthermic strand with the other anomalous hyperthermic area in the projection of sacrum and lumbar spine, which is a possible projection of the primary focus. The difference in temperature between the thermal strand and the adjacent tissues ($\Delta T \approx 3$ °C) can be estimated by thermal cross section (Fig. 6, *c*) indicated by white arrow on the thermogram fragment.

Thermal strands have been observed in approximately 25% of patients with different types, stages, and localizations of tumors before and during RT treatment. Observations of the dynamics of thermal strands in the course of RT treatment have showed that the location and temperature parameters of the strands practically do not change as a result of irradiation, even if a significant regress of tumor is reported [4].

CONCLUSIONS

Despite a huge potential of medical thermography as remote, non-invasive, cheap and patient-friendly method of functional analysis, for the time being, the method has been used only for a local projection and is still «raw», underdeveloped and has not brought to clinical use. The main reason for this situation is the lack of knowledge about physiological background of thermal images. Therefore, any new information obtained from thermographic studies of the dynamics of human thermal fields is important and relevant.

Based on the thermographic survey of 70 patients with oncological diseases before and in the course of radiation therapy the following results and information have been obtained:

1. Identification by the criterion of thermal asymmetry of hyperthermic areas in the projection of tumors in patients before the start of RT treatment has showed that:

- In all patients with breast cancer large hyperthermic areas with significant thermal asymmetry have been detected, which confirms the diagnostic capacity of the thermal method for this type of tumors;
- Significant thermal asymmetry has been reported on the skin in the projection of lymphomas and affected lymph nodes;
- Low detectability of thermal imprints of other tumors testifies to the limited capacity or even ineffectiveness of thermal diagnostics with respect to majority of internal neoplasms.
- No correlation between the tumor dispersion (extent) and the intensity of anomalous thermal field on the skin in the tumor projection has been detected.

2. The results of quantitative and statistical analysis of changes in anomalous thermal fields in the sites of interest in the course of RT treatment obtained for a sample with low statistical power (a group of 19 patients) have showed that:

- Adequate correlation ($R \approx 0{,}75 \div 0{,}83$) of thermal parameters and level of clinical mucositis factor;

✦ «Good quality» (AUC = 0.79) of proposed method for prediction of individual mucositis level based on established fact that the anomalous thermal field in certain areas appears before clinical symptoms of mucositis manifest themselves;

3. An expected decrease in temperatures of thermal imprints of tumors due to RT has been reported only for lymphomas and affected lymph nodes. In other cases, only an increase in temperature is observed because of development of local radiation reactions (the irradiated area in all cases coincided with the area of the tumor thermal imprint).

4. Thermal strands have been observed in approximately 25% of patients with different types, stages, and localizations of tumors before and during RT treatment. Observations of the dynamics of thermal strands in the course of RT treatment have showed that the location and temperature parameters of the strands practically do not change as a result of irradiation, even if a significant regress of tumor is reported.

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РЕЗУЛЬТАТИ ДОСЛІДЖЕННЯ АНОМАЛЬНИХ ТЕПЛОВИХ ПОЛІВ ЛЮДИНИ ПРИ ОПРОМІНЕННІ

Наведено результати термографічних досліджень теплових полів на поверхні шкіри пацієнтів з онкологічними захворюваннями при опроміненні пухлин. Запропоновано кількісний і статистичний підхід до аналізу теплових зображень. Результати термографічного обстеження пацієнтів до початку опромінення свідчать про обмеженість або навіть неможливість тепловізійної діагностики більшості внутрішніх новоутворень. З іншого боку, отримані коефіцієнти кореляції $R = 0{,}76 \div 0{,}81$ між тепловими параметрами і клінічними показниками рівня побічних реакцій, а також отриманий показник «гарна якість» методу термографічного прогнозування свідчать про можливість використання термографії для контролю і прогнозування рівня побічних реакцій при опроміненні. Відмічена необхідність збільшення статистичної потужності аналізованих вибірок.

Ключові слова: термографія, злоякісна пухлина, променева терапія, побічні реакції.

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РЕЗУЛЬТАТЫ ИССЛЕДОВАНИЯ АНОМАЛЬНЫХ ТЕПЛОВЫХ ПОЛЕЙ ЧЕЛОВЕКА ПРИ ОБЛУЧЕНИИ

Приведены результаты термографических исследований тепловых полей на поверхности кожи пациентов с онкологическими заболеваниями при облучении опухолей. Предложен количественный и статистический подход к анализу тепловых изображений. Результаты термографического обследования пациентов до начала облучения свидетельствуют об ограниченности или даже невозможности тепловизионной диагностики большинства внутренних новообразований. С другой стороны, полученные коэффициенты корреляции $R = 0{,}76 \div 0{,}81$ между тепловыми параметрами и клиническими показателями уровня побочных реакций, а также полученный показатель «хорошее качество» метода термографического прогнозирования, свидетельствуют о возможности использования термографии для контроля и прогнозирования уровня побочных реакций при облучении. Отмечена необходимость увеличения статистической мощности анализируемых выборок.

Ключевые слова: термография, злокачественная опухоль, лучевая терапия, побочные реакции.