

Potential Use of Novel Image and Signal Processing Methods to Develop a Quantitative Assessment of the Severity of Acute Radiation Dermatitis in Breast Cancer Radiotherapy

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Abstract: More than 95% of patients who undergo radiotherapy report symptoms of radiation dermatitis, which is a side effect of this therapy. Erythema, edema, dry and moist desquamation intensify with each fraction of irradiation and can significantly reduce a patient's quality of life. Therefore, an effective skin care procedure is needed for skin that has been exposed to ionizing radiation in order to avoid unplanned treatment interruptions. The methods that are currently used to assess the severity of an acute radiation reaction are based on visual scales (RTOG, EORTC, NCI CTCAE, LENT-SOMA). Because the assessment is made subjectively, the results depend on the researchers, their experience and perceptiveness. Until now, several studies have been carried out to check the possibility of using an objective methods like hyperspectral imaging, thermal imaging, laser Doppler flowmetry, dielectric and electrochemical methods, reflection spectrophotometry and Courage-Khazaka Multi-skin instrument to radiation-induced dermatitis assessment. Unfortunately, due to various limitations that occurred in the research, none of these techniques was successfully implement as alternative for visual assessment. The continuous development of technology enables researchers to access new techniques that might constitute useful diagnostic and cognitive tools. Infrared thermal imaging, hyperspectral imaging and reflectance spectroscopy are examples of the visual techniques that have been used for many years in various fields of medicine, including dermatology and chronic wound or burn care. They provide information on the skin parameters, such as the temperature, concentration and distribution of chromophores (eg, hemoglobin and melanin), saturation or perfusion changes. The aim of this study is to review the available literature on the use of imaging methods in the clinical assessment of skin with lesions of various origins, evaluation of their suitability for the assessment of radiation reaction and consideration the possibility of creating a quantitative scale for assessing severity of acute radiation dermatitis.

Keywords: infrared thermal imaging, hyperspectral imaging, reflectance spectroscopy, breast cancer, radiodermatitis, algorithm

Introduction

According to the data provided by WHO, there were more than 19.2 million cases of cancer in 2020. Breast cancer is the most common malignant neoplasm that accounts for approximately 2.3 million cases and is also the most common cancer death in the female group of patients (almost 690,000 deaths).¹ The cause of the occurrence of neoplastic changes are not clearly defined but based on state of the current knowledge, it is a result of the interaction of various risk factors such as environmental, exogenous and endogenous factors as well as individual factors (genetic predisposition) that increase the risk of getting the disease. The most frequently mentioned causes of cancer include smoking, alcohol abuse, a high fat diet and a lack of physical activity.^{2,3}

The choice of the treatment method depends on the patient's performance status, the clinical stage of the neoplastic disease, the histopathological diagnosis, the biological subtype of the neoplasm and any coexisting diseases. The diagnostic and therapeutic plan is developed by a Multidisciplinary Team.^{4,5}

Radiotherapy (RT) is one of the basic methods that is used to treat patients with neoplastic disease in addition to surgical and systemic treatment (chemotherapy, hormone therapy, immunotherapy). Approximately 50% of patients with various types of cancer will undergo RT as part of their treatment. Ionizing radiation treatment is most often used as part of adjuvant treatment in patients with breast cancer after a radical mastectomy or breast conserving surgery (BCS).^{6,7} Planning the radiotherapy is a multi-stage process that requires the involvement of a team of specialists and the use of technologically advanced medical equipment. Quality control procedures are used to prepare the radiotherapy plan and treatment delivery in order to ensure the safe implementation of the treatment plan in accordance with international standards.^{7,8}

The aim of radiotherapy is to deposit the prescribed dose of ionizing radiation in the indicated area while limiting the maximum dose in normal tissues (heart, lungs, contralateral breast). Breast RT uses both external beam irradiation and brachytherapy (irradiation using a radiation source that is placed inside the treated area). Depending on the stage of the neoplastic disease, the scope of the surgical treatment and the postoperative pathomorphological diagnosis, the irradiated area may include the chest wall, the breast, the tumor bed and the regional lymphatic system (supraclavicular area, axillary fossa).^{7,9}

A standard course of RT usually last for four to five weeks (five fractions per week) and consists of 25–28 fractions of single doses 1.8–2.0 Gy, which is enhanced by an additional boost of 10–16Gy to the tumor bed after a lumpectomy. In recent years, many institutes have introduced hypofractionation regimens in which a single dose >2.0 Gy is delivered in 15–18 sessions. This treatment reduces the time of exposure to ionizing radiation with the same clinical results as conventionally fractionated RT, which makes it easier for patients to complete the course of RT.^{8–10}

Despite the undeniable advantages of radiotherapy, which include its loco-regional control, high efficiency and safety profile, more than 95% of patients report side effects that may significantly reduce their quality of life. These radiation-associated side effect such as erythema, edema, dry and moist desquamation, itching, soreness or even necrosis are known as radiodermatitis (RD).^{11–13}

The early symptoms refer to the place that has been directly exposed to ionizing radiation and are called acute radiation dermatitis (ARD). They can occur in as little as during the first four weeks of radiotherapy and then increase with each fraction. The late side effects of RT can appear months or even years after the course of RT and is called chronic radiation dermatitis.^{14,15}

In the first stage, ARD is manifested by redness of varying severity along with the dry or wet desquamation of the epidermis. Exfoliation of the epidermis reveals a defect in the cells of the basal layer of the epidermis as well as in the sebaceous and sweat glands in the dermis. Wet exfoliation is accompanied by serous exudate and a loss of the dermis. Late RD is manifested as changes in vascularity (telangiectasia), dermis atrophy, changes in pigmentation (poikiloderma, hyper- or hypopigmentation), fibrosis, ulceration or necrosis. The severity of chronic radiodermatitis depends on the total radiation dose, the size of the irradiated area and the individual predisposition of patient.^{14,16,17}

The severity of skin changes also depends on many other factors, including the type and energy of the radiation, the total dose, the duration of therapy, the power and number of fractional doses as well as the sensitivity of the irradiated cells and the individual predisposition of patients. The assessment of the skin condition is based on the subjective assessment of the oncologist and is most often presented using a visual scale. In the case of ARD, the most commonly used scales are The European Organization for Research and Treatment of Cancer (EORTC), the Radiation Therapy Oncology Group (RTOG) and the five-point scale of the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI CTCAE, version 5).^{18,19} The Late Effects on Normal Tissue – Subjective, Objective Management and Analytic (LENT-SOMA) scale is used to determine the severity of chronic RD.²⁰ A comparison of most commonly used scales is presented in [Table 1](#).

Visual assessment of the condition of the skin depends on many factors but the most important of which are experience and perceptiveness of researcher. Due to the lack of objective methods of assessing ARS, which do not allow to quantify the physiological skin parameters, several studies have been carried out using alternative quantitative methods. Kitajima et al used the Multi-skin Instrument (Courage + Khazaka Corporation) to assess the condition of the skin during radiotherapy. It allows to check the surface temperature of the skin, the level of hydration and the intensity of melanin and erythema. The results of these preliminary studies indicate that corneometer, mexameter and skin-thermometer measurements can be an objective tool to improve the accuracy of skin assessment.¹⁸ Sanchis et al used the technique of laser Doppler flowmetry (LDF) to measure cutaneous blood flow in patients with breast cancer undergoing RT. The results of this study indicate that measurements with LDF could be

Table I A Comparison of the Scales That are Used to Determine the Severity of Acute and Chronic RD^{18–20}

Grade	RTOG	NCI CTCAE v.5.0	LENT-SOMA
0	Normal skin, no visible symptoms		
I	Follicular, faint or dull erythema epilation dry desquamation decreased sweating	Faint erythema dry desquamation	Occasional and minimal pain, symptomatic edema, barely palpable, increased density of the fibrosis, telangiectasia <1cm ² , 2–4cm arm edema, epidermal ulceration (<1cm ²), atrophy 10–25%
II	Tender or bright erythema patchy moist desquamation that is confined to the skin folds moderate edema	Moderate to brisk erythema patchy moist desquamation that is confined to the skin folds and creases moderate edema	Intermittent and tolerable pain, asymptomatic edema, definite increased density and firmness of the fibrosis, telangiectasia 1–4cm ² , 4–6cm arm edema, dermal ulceration (>1cm ²), Atrophy >25–40%
III	Confluent, moist desquamation in areas other than in the skin folds pitting edema bleeding may occur	Moist desquamation in areas other than in the skin folds and creases bleeding that is induced by a minor trauma or abrasion	Persistent and intense pain secondary dysfunction edema, very marked density, retraction and fixation of fibrosis, telangiectasia >4cm ² , >6cm arm edema, subcutaneous ulceration, atrophy >40–75%
IV	Ulceration hemorrhage and necrosis	Skin necrosis or ulceration of full thickness in the dermis, spontaneous bleeding from the involved site	Refractory and excruciating pain, unable to move the arm, exposed bone, necrosis, atrophy on entire breast
V	The intensity of the reaction was not determined	Death	The intensity of the reaction was not determined

useful and objective method to assess RD.²¹ Research has also been carried out using thermal imaging techniques to assess radiodermatitis. Obtained by Maillot et al results confirm the increase in local skin temperature during the development of the radiation-induced inflammatory, however, due to the limitations of this study, further research is needed on this issue.²² Abdlaty et al conducted a pilot study to use hyperspectral imaging to assess the erythema that develops during skin cancer treatment with radiation therapy. The obtained results indicate that HSI allows for the quantification of oxygenation and perfusion of the skin subjected to radiotherapy and can be approached to objectively assess the severity of erythema.²³

Despite numerous studies using various measurement techniques, at present researchers do not have at their disposal a standardized method allowing for an objective assessment of the degree of the severity of the radiation reaction. Further research on this topic is necessary because only repeated measurements and sensitive techniques will allow for early identification of RD lesions, their prevention and effective treatment.

Materials and Methods

In order to analyze the suitability of the imaging methods that are used to assess the intensity of a radiation reaction, the research was conducted in the PubMed electronic database, which was searched for any articles that were published between 1991 and 2021. The search was conducted until December 5, 2021. The language of the articles was limited to English and the databases that were used had the appropriate filters. The following keywords were searched in various combinations in order to optimize the search results in accordance with the topic of this article: infrared thermal imaging, thermography, hyperspectral imaging, reflectance spectroscopy, skin, wound care, and diagnosis. All of the articles that were cited in these narrative review were also screened in order to identify any other potential studies in their reference lists.

Results

During the online search, the articles were screened by their titles and abstracts. A total of 39 articles were considered to be relevant and were selected for a full-text reading. A scan of the literature and citations of the included studies yielded 18 more articles for a full-text reading. Among the 57 papers that were considered for the present review, 17 did not have

any relevant data for the planned narrative review and were excluded. The remaining 40 articles, among which were reviews, case studies, randomized controlled trials, the content was evaluated and selected for the data analysis.

Discussion

Infrared Thermal Imaging

Because changes in the skin temperature are one of the earliest observed disease symptoms of organisms infrared thermal imaging (IRT) analysis can be one of the basic diagnostic and cognitive tools. IRT enables information about the physiological and pathological processes that take place in the human body to be obtained by analyzing the temperature gradient, its change over time and its distribution in a given area. Importantly, it is a non-invasive and non-contact analysis, which is absolutely harmless, does not cause any side effects, and therefore can be used for prolonged or repeated diagnostics.^{24,25} The basis of IRT is the fact that the temperature that is measured on the body surface depends on the temperature of the internal organs and the tissues under the skin. Since lesions very often change the heat flux that is emitted by diseased tissue, it causes changes in the temperature of the surrounding tissues, including the skin. In the case of a thermographic analysis, it is important that the reference point is an area of the patient's skin that has not been affected by the disease because body temperature depends on many factors, including age or gender, thanks to which differences in its values can be observed during the measurements.²⁶

IRT has been used in many areas of medicine. One of the oldest uses was for diagnosing breast cancer. In the 1950s, Lawson conducted research that proved its usefulness for diagnosing benign neoplastic changes in the breast.²⁷ In later years, numerous studies were conducted that confirmed the usefulness of thermography in diagnosing the early stage of breast cancer. Although thermography cannot show the morphological structure of the breast, it does illustrate the thermal changes and changes in the blood vessels in tissues, which are usually the first symptoms of a developing neoplastic disease.²⁸ Because of the development of technology and temperature measurement standards (ISO, ASTM – Table 2) that define the specifications for measuring devices, including their minimum requirements, equipment calibration and the practical aspects of taking

Table 2 Summary of the Basic Standards for a Thermal Imaging Analysis

No.	Norm/Standard Number	Title
1	ISO 80601-2-56:2017	Medical electrical equipment — Part 2–56: Specific requirements for the basic safety and essential performance of clinical thermometers for measuring body temperature ⁴⁵
2	IEC 80601-2-59:2017	Medical electrical equipment — Part 2–59: Specific requirements for the basic safety and essential performance of screening thermographs for human febrile temperature screening ⁴⁶
3	ISO/TR 13154:2009	Medical electrical equipment — Deployment, implementation and operational guidelines for identifying febrile humans using a screening thermograph ⁴⁷
4	ASTM E1213-14 (2018)	Standard Practice for Minimum Resolvable Temperature Difference for Thermal Imaging Systems ⁴⁸
5	ASTM E1311-14 (2018)	Standard Practice for Minimum Detectable Temperature Difference for Thermal Imaging Systems ⁴⁹
6	ASTM E1543-14 (2018)	Standard Practice for Noise Equivalent Temperature Difference of Thermal Imaging Systems ⁵⁰
7	ASTM E1256-17	Standard Test Methods for Radiation Thermometers (Single Waveband Type) ⁵¹
8	ASTM E1862-14 (2018)	Standard Practice for Measuring and Compensating for Reflected Temperature Using Infrared Imaging Radiometers ⁵²
9	ASTM E1933-14 (2018)	Standard Practice for Measuring and Compensating for Emissivity Using Infrared Imaging Radiometers ⁵³

the measurements, thermography is increasingly used in medicine. IRT is currently used in practice, among others, in dentistry to assess the condition of the periodontium in patients with leukemia, to assess inferior alveolar nerve deficits or to screen for endodontic diseases in the oral cavity.^{29–31} It is used to diagnose pneumonia and also supports diagnosing thyroid diseases.³² In cardiology, it can be used to monitor the circulation or heart during cardiac surgery, while in allergology, it supports diagnosing respiratory and food allergies.^{33–35} It was also found that a thermal imaging analysis can be an effective tool for diagnosing peripheral vascular disorders.²⁸

IRT is also a useful technique for imaging the skin temperature distribution in diabetics.³⁶ The studies that were conducted by Bagavathiappan et al confirmed that thermal imaging can be used to detect diabetic neuropathy while the studies that were conducted by Aliahmad et al confirmed the usefulness of IRT for evaluating the healing status of diabetes-related foot ulcers.^{37,38} Because most skin disorders cause inflammation that is manifested by changes in temperature, IRT can be considered to be a suitable technique to use to evaluate it. Vargas et al used the thermography method to diagnose leprosy and to evaluate the effectiveness of the treatment.³⁹ In the case of dermatological diseases, thermal imaging has been used in studies of psoriasis, inter alia, for the early diagnosis of psoriatic arthritis.⁴⁰ According to the studies of Thomas et al, IRT can also be used to optimize the application of a laser during laser-based skin treatment such as depilation or treating vascular lesions.⁴¹ Numerous studies have been conducted to confirm the usefulness of thermography for treating burns. This technique can be used to assess the depth of the burns as well as to qualify patients who require early surgery. The effectiveness of sprayed and poured cooling agents was also compared for the initial cooling management of extensive burns.^{25,42–44}

The development of computer technologies, the use of high-resolution detectors and the development of measurement standards have made thermography increasingly popular in the scientific community. Because thermal imaging cameras are widely available and easy to use, the techniques can be used by both scientific laboratories and medical centers.

Hyperspectral Imaging

Hyperspectral imaging (HSI), which is derived from standard digital photography, is an increasingly popular method of imaging using visible light. This technique uses three wavelength ranges that correspond to the red, green and blue channels to record an image that consists of many individual photos that are recorded at a strictly defined wavelength.⁵⁴ Because of the high spectral resolution, the recorded data is presented as a two-dimensional map of the reflection spectra, which enables a quantitative analysis of a given object by, eg, color measurement or qualitative by, eg, identifying chemical compounds. The obtained set of images is called a hypercube and its analysis can be used to determine the concentration of tissue chromophores.⁵⁵ It is important to keep in mind that these reflectance spectra of the skin can be affected by different factors such as the melanin concentration, the thickness of the epidermis, the oxygen saturation of the blood in the dermis or blood volume.⁵⁵

Taking pictures with a hyperspectral camera is non-invasive and non-contact causes no side effects, and therefore it is used more frequently in various fields of medicine, especially in dermatology.⁵⁶ This technique enables, inter alia, the differences in the absorption of visible light radiation by the chromophores in the skin such as hemoglobin and melanin to be analyzed, which makes it possible to determine their distribution and concentration in a given area of the skin.⁵⁷

The studies that were conducted by Chin et al and Shah et al indicated that HSI analysis can be used to visualize and quantify changes in oxygenation and perfusion in the areas of the skin that have been exposed to ionizing radiation. Such an assessment is possible immediately after irradiation before any visible skin lesions appear, which can be a useful tool for the immediate assessment of the condition of patients who have had radiation accidents.^{58,59} Several studies have been conducted on the use of hyperspectral methods to control and evaluate the healing process of chronic wounds. Until now, these processes have been monitored by a visual inspection, which is a subjective method the result of which depends on the experience and perception of the examiners. The studies that were conducted by Calin et al showed that HSI enables the different types of tissue that are present in the injured area to be identified, which enables an objective wound characterization to be made.⁶⁰ The research proved that hyperspectral imaging enables the tissue saturation and hydration as well as the observation of blood flow to be determined, and therefore it can be used for the local detection of changes in perfusion and oxygenation, which are extremely important in open wound healing.^{54,60} Yudovsky et al used hyperspectral methods to control and evaluate the healing process of diabetic foot ulcerations, which occur as

a complication in 15–25% of patients with type 1 and type 2 diabetes. What is also important is that HSI can be used to assess the risk of ulceration as early as during screening and not during the months of observation as is the case today.⁵⁵ The case report presented by McCarthy et al indicated that HSI might also be an effective method for determining the depth of a burn, which potentially enable a decision about early surgical intervention.⁶¹

HSI has also been used with oncology patients. The research of Kho et al indicated the possibility of using HSI as a safe and precise tool for determining the margin of safety during BCS.⁶²

Diffuse Reflectance

Diffuse reflectance (DR), which uses radiation with a wavelength of 250–2500 nm, has found wide application in analyzing various surfaces and materials.^{63,64} A reflectometer measures the absorption and transmission of the emitted radiation and determines its reflectance. Using the obtained data and the optical properties of a surface, it is possible to obtain information on the structure of the tested sample or on the concentration of chromophores.

DR is widely used in many fields of technology and pharmacy, and it has also been used in medicine to study the properties of the skin. By measuring reflectance, quantitative data on the melanin and hemoglobin content of the skin can be obtained, which might be useful in detecting acute and chronic inflammations that are caused by various factors, eg, an infection or irritation. The studies that were conducted by Yudovsky et al showed that a method that uses reflectance measurement can be a useful tool for monitoring changes in the blood supply and melanin concentration in the skin as well as for analyzing the epidermal thickness, which is associated with the normal aging process of the skin and is caused by external factors (UV radiation) and disease states (ulceration, cancer).^{65,66} The results of a study conducted by Kollias et al in 1995 showed that diffuse reflectance spectroscopy enabled the erythema that is caused by an irritant (sodium lauryl sulfate) to be evaluated. DR enables the apparent concentration of oxyhemoglobin to be assessed. Studies have confirmed that irritant-induced inflammation primarily involves the capillaries and the superficial arterial plexus.⁶⁷ Additionally, the research that was conducted by Riordan et al indicated that DR can be used to design an algorithm for detecting erythema in skin with varying pigmentations.⁶⁸ As was shown by a pilot study that was conducted by Tzeng et al, reflectance can also be used to diagnose or evaluate the skin of psoriasis patients without having to perform a histopathology examination, which is invasive.⁶⁹ DR was also used by Hsu et al to assess the severity of keloid scars. That research indicated that this technique can be used to objectively evaluate the alignment direction of collagen bundles in scars as well as to quantify the concentration of collagen, water content and oxygen saturation in order to monitor the response to the therapeutic interventions.⁷⁰

Conclusion

Considering that a visual assessment of most dermatological changes is a subjective evaluation by the researcher, the lack of standardization and comparability of the results due to the inter-individual differences and personal changes in research teams, in many cases, such an analysis does not reflect the actual state of the patient, which prevents the precise planning of further treatment. In the case of RD, an appropriate assessment of the developing inflammation is of essential importance in enabling clinicians and researchers to provide effective patient care. The appropriate start of the treatment can in many cases determine the possibility of completing the course of radiotherapy.

As can be seen from the summary presented in Table 1, the scales that are used to determine the intensity of the radiation reaction are based solely on a visual evaluation, and thus depend on the subjective assessment of the researchers, which depends on their experience, perceptiveness and the information that is obtained from a patient during a follow-up visit. Therefore, depending on the physician and the institute in which the therapy is performed, there may be discrepancies in assessing the severity of the side effects of RT. This makes it difficult to assess the effectiveness of the treatments given to patients and to compare the effectiveness of the active ingredients and care preparations that are analyzed in studies that are conducted by various institutes.

Therefore, it is important to develop and implement objective methods for assessing the condition of the skin that has been affected by RD using numerical data that is independent of the researcher. For this purpose, imaging methods, which have been gaining popularity for many years and are increasingly being used in dermatological diagnostics, can be useful for both clinical research and medical care.

As the analysis shows, the above-mentioned methods have been used for years to determine the temperature of the skin (IRT), erythema and to analyze wounds, including those associated with burns (HSI, DR), which makes them perfectly suitable to dealing with the problem of ARD. Using HSI and DR, it is possible to determine the concentration and distribution of hemoglobin and melanin in the skin. In the case of RD, which is manifested by erythema and pigmentation changes, these chromophores will be the basic parameter that indicates the development and severity of the ARD. Analyzing them will also be useful for monitoring a patient's recovery after RT. In the case of RD, which is an inflammation reaction of the skin, the data that is obtained from the thermal imaging analysis would be also useful. Temperature changes, which are usually the first observed symptoms of a disease, indicate the development of a reaction. Therefore, it seems reasonable to combine these three techniques and to supplement the data that is obtained with observations according to the visual methods in order to create an algorithm for quantifying the severity of the ARD. The use of imaging methods is also supported by the increasing availability of equipment such as hyperspectral cameras, thermal imaging cameras and diffuse reflectometers, which means that the methods can be widely used. Each of these methods is non-invasive, non-contact and safe for patients, so they can safely be used as a diagnostic tool during the follow-up visits during radiotherapy and after its completion. However, it should be noted that HSI and DR are relatively young techniques that are continuously being researched in various fields of medicine, and that therefore they require standards for the methods for specific applications be established and developed.

Until now, several studies have been carried out to check the possibility of using new objective methods to assess the severity of the radiation reaction. Researchers focused on methods such as thermal imaging, laser Doppler flowmetry, dielectric and electrochemical methods, reflection spectrophotometry and used Courage-Khazaka Multi-skin instrument equipped with different probes like skin-thermometer, corneometer and mexameter. The results obtained from all these studies indicate that instrumental methods, including optical techniques, can be used to assess the changes taking place in the skin exposed to radiation, and therefore they can be an alternative to visual assessment. Unfortunately, due to various limitations that occurred in the studies, including too small research groups, it was not possible to develop and validate a final method that could successfully replace visual evaluation so further researches are required.

Because of the development of technology and the widespread availability of the equipment, these imaging techniques can be a valuable diagnostic and cognitive tool in evaluating RD and determining the effective skin care procedure.

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Disclosure

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