Dynamic infrared imaging of cutaneous melanoma and normal skin in patients treated with BNCT


Abstract

We recently initiated a program aimed to investigate the suitability of dynamic infrared imaging for following-up nodular melanoma patients treated with BNCT. The reason that makes infrared imaging attractive is the fact that it constitutes a functional and non-invasive imaging method, providing information on the normal and abnormal physiologic response of the nervous and vascular systems, as well as the local metabolic rate and inflammatory processes that ultimately appear as differences in the skin temperature.

An infrared camera, with a focal plane array of 320 x 240 uncooled ferroelectric detectors is employed, which provides a video stream of the infrared emission in the 7–14 μm wavelength band. A double blackbody is used as reference for absolute temperature calibration.

After following a protocol for patient preparation and acclimatization, a basal study is performed. Subsequently, the anatomic region of interest is subjected to a provocation test (a cold stimulus), which induces an autonomic vasoconstriction reflex in normal structures, thus enhancing the thermal contrast due to the differences in the vasculature of the different skin regions. Radiation erythema reactions and melanoma nodules possess typically a faster temperature recovery than healthy, non-irradiated skin. However, some other non-pathological structures are also detectable by infrared imaging, (e.g. scars, vessels, arteriovenous anastomoses and injuries), thus requiring a multi-study comparison in order to discriminate the tumor signal. Besides the superficial nodules, which are readily noticeable by infrared imaging, we have detected thermal signals that are coincident with the location of non-palpable nodules, which are observable by CT and ultrasound. Diffuse regions of fast temperature recovery after a cold stimulus were observed between the third and sixth weeks post-BNCT, concurrent with the clinical manifestation of radiation erythema. The location of the erythematous visible and infrared regions is consistent with the 3D dosimetry calculations.

1. Introduction

Medical infrared (IR) thermography is based on the derivation of the spatial and temporal pattern of temperature associated to the IR radiance emitted by the tissue under study. This distribution not only depends on physical parameters, but also on the physiology associated to the homeostatic and metabolic processes and the structure and dynamics of the vascular, tissular and nervous systems. It is affected by internal and external factors and, in the case of the skin, its spatial and temporal evolution is the manifestation of the human thermoregulatory system in an attempt to preserve the body temperature, by controlling the rates of heat production and heat loss.

The particular tumor architecture and angiogenesis processes lead to a very dissimilar situation. Inflammation, metabolic rate, interstitial hypertension, abnormal vessel morphology and lack of response to homeostatic signals are some of the differences that make tumors to behave differently than normal tissue in terms of heat production and dissipation.

Application of IR thermography for the study of malignant melanoma (MM) has been described by an Italian group (Di Carlo, 1995). They employed a cold patch applied onto the affected area,
temperature calibration, a double-cavity black body is used. One
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2. Materials and methods

2.1. Infrared detection equipment

An IR camera (Raytheon PalmIR 250, L3 Comm. Systems) is
ployed, which uses uncooled ferroelectric detector technology,
sensitive to IR radiation in the 7–14 μm wavelength band. It
focuses targets located within 1.5 and 3 m distance. The detector
is a focal plane array (FPA) composed of 320 × 240 barium–stron-
tium titanate (BST) ceramic elements. The IR camera provides a
video output signal suitable for time-dependent studies. For
temperature calibration, a double-cavity black body is used. One
of the cavities is electrically heated to temperatures about 40 °C
and the other one is in equilibrium with ambient temperature.

2.2. Protocols in clinical thermography

Clinical thermography is based on the observation of the
functional aspects of body thermal regulation. However, environ-
mental, pharmacochemical, mechanical and even emotional stres-
sors are capable of inducing changes in the skin temperature.
Thus, a series of standards and protocols in clinical thermography
are followed in our studies for the correct application and
interpretation of the results (IACT).

2.3. Provocation tests

Two different cold stimuli were employed: immersion in water
at 15 °C for 2 min or alcohol spray followed by fan currents over
the region. The latter, which induces cooling by forced evapora-
tion, was used when immersion was not feasible and the skin
evidenced no signs of damage. However, since radiation may
induce changes in the skin permeability and can produce severe
damage, a system capable of generating cold air currents is
presently under design, thus avoiding any contact with the skin of
the patient.

2.4. Thermographic procedure

Before the IR study start, the patient remains at rest for a
period of 15–20 min in order for the region to be examined to
reach an approximate steady physiologic state of thermal
equilibrium. This is accomplished by exposing the area to the
ambient conditions. After that period, a 30-s basal study is
performed to record the initial temperature distribution. Subse-
quently, a cold stimulus is applied and another video is acquired
for 3 min or more.

Since it is important to compare basal with post-stimulus
temperature distributions, the region to examine is immobilized
and anatomical landmarks are used for image registration.

2.5. Clinical cases

The first case is a 72 years old woman (patient ID: IRP-1) with a
history of MM, Breslow 3 mm, Clark 3 at the moment of diagnosis,
with several loco-regional relapses as subcutaneous nodules
through 10 years of follow-up, treated with surgical resection
every time. BNCT was performed on May 17th, 2007, for two
subcutaneous nodules in the right thigh. Complete response was
observed at the first assessment, with grade 1 cutaneous toxicity
(erythema).

The second patient (IRP-2) is a 66 years old male diagnosed in
2004 for MM, Breslow 3.5 mm, Clark 3, in the left foot. He had
presented several local relapses treated with surgical approaches.
At the moment of BNCT the patient had multiple subcutaneous
nodules in the external maleolar region of the left foot. He was
treated by BNCT on June 29th, 2007. Three out of 10 nodules
developed an objective response. The other nodules had no
change after the treatment. The patient presented cutaneous
toxicity grade 3 (ulceration), treatment-related.

Both patients were treated at the BNCT facility of the RA-6
reactor, Bariloche, Argentina. The patients were followed by
clinical inspection, CT and high-resolution Doppler ultrasound.
IR studies were carried out before BNCT, weekly during the first
month after the treatment, and then monthly.

Evaluation of the skin reaction was performed by the clinician
during follow-up. Additionally, in order to obtain a semi-
quantitative measurement, an algorithm (Schaef er et al., 2006)
was implemented to discriminate human skin employing visible
images. Briefly, skin hue values lie in a narrow range, and thus
small variations of skin color can be visualized by extracting the
hue channel from RGB images.

2.6. Thermographic figure of merit for evaluating the skin reaction

During the application of a cold stimulus, the skin temperature
drops forced by the change in the boundary condition. After
the end of the stimulus, skin temperature will evolve depending on
the local heating sources, which, as explained before, can be of
diverse nature. Let ΔT(Xm, dn) be the temperature difference
between basal and tm,s after the end of the cold stimulus,
measured the day dn in a given skin region. A quantity suitable
for comparing studies is proposed

\[
\alpha(t_m, d_n) = (\Delta T_{ref} - \Delta T_X)/\Delta T_{ref} |_{t_m,d_n} 
\]  

where \( \Delta T_{ref} \) and \( \Delta T_X \) are the temperature differences of a reference
skin region and a particular region X, respectively. It is important
to remark that this quantity is independent of the camera gain and
offset values, and thus is comparable between different days.

Fig. 1. Selected regions (patient IRP-1) on the skin: (A) and (B) are regions within
the treatment field (skin dose greater than 16 Gy-Eq); (C) is a region of low skin
dose (less than 2 Gy-Eq). 3D dose reconstruction performed with the sphere code
(Gossio et al., 2008).
2.7. 3D computational dosimetry

Based on the data involved in a BNCT melanoma treatment, 3D representations of the dose distribution in the skin can be performed using the Sphere code (Gossio et al., 2008). These reconstructions allow to easily visualize regions of different doses in the skin for studying local toxicities as well as tumor control. Using this tool, a registration of the 3D reconstruction and thermograms of the patient anatomy can be performed to spatially correlate the information provided by DIRI with absorbed dose.

2.8. Selected regions for evaluation of the skin reaction and tumor temperature

A reference skin region in the thigh of patient IRP-1 that received a non-therapeutic dose was selected, free from surgical scars and distant from the diagnosed melanoma nodules. In order to correlate the erythematous reaction with some thermal signature, skin regions within the treatment field were chosen, at least 1-cm distance from scars and nodules (Fig. 1). Every region must be identifiable in all IR studies.

The nodules of patient IRP-2 were clearly detectable by visual inspection. For the IR studies, a series of regions close to the larger MM nodules (5–8 and 10) were studied, as well as a normal skin region for comparison (Fig. 2).

3. Results

3.1. Evolution of the erythematous reaction

Fig. 3 shows the evolution of the quantity given by Eq. (1) during the initial follow-up period (30 weeks) for patient IRP-1, together with the relative difference of hue values.

A marked increase is evident at 22 days after BNCT, concomitant with the observed skin color changes. It can be seen that the peak value exceeds unity, because the skin temperature 1 min after the cold stimulus within the irradiation field was actually higher than its basal temperature. The same analysis made for the surgical scars within the field revealed identical behavior.

3.2. Temperature recovery in MM after cold stimulus

Fig. 4 shows the evolution of temperature in selected regions (N5, N8, N10, ROI 5–8 and normal skin) for patient IRP-2, after the cold stimulus (15 °C water immersion for 2 min). It is worthy to note that at the beginning of the study, the temperature of the regions in the proximity of the nodules was already 6–10 °C higher than normal skin, and their temperature recovery was much faster than normal tissue.

The region ROI 5–8 contains tumor as well as normal skin, and its temperature is still higher than the normal tissue temperature,
but increases slower than the nodules. Fig. 5 shows a registration between visible and IR images.

3.3. Comparison of DIRI with other studies

Table 1 shows a comparison between the detection results of computed tomography, Doppler ultrasound and DIRI, for patient IRP-2. We can see that DIRI has higher sensitivity than Doppler ultrasound and similar to CT.

4. Conclusions

These preliminary results show that dynamic IR imaging could be a useful and sensitive tool to study skin toxicities and tumor...
control in BNCT melanoma treatments. In contrast with conventional radiotherapy, BNCT for malignant melanoma is characterized by highly non-uniform dose distributions in the skin. One of the purposes of this work is to investigate by means of DIRI the correlation between the spatial extension of the acute skin reaction and the superficial dose distribution, in order to better determine tolerance doses and therefore to optimize the treatment. In addition, given the capacity of DIRI to observe the functional aspects of tissues, the technique can help to locate abnormally high temperature regions as well as melanoma nodules that are virtually invisible in CT images, owing to their small contrast differences with respect to normal tissue. The results of these investigations can be potentially useful in other fields of research beyond BNCT, e.g., radiation accidents assessment or as an adjunct imaging method for the study of melanoma patients treated with other modalities.

References

