Finding postirradiation reaction in lungs from digitized X-rays

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Abstract. A quantitative measure of the postirradiation reaction in the lung tissue, based on the concept of the equivalent absorber thickness (EAT), has been estimated on the basis of the series of X-ray images of lungs. Radiation effect in normal lung tissue is of major interest in the combined modality treatment of cancer. The proposed method of estimating the EAT from X-ray images consists in comparing the digitized image of the tested radiograph with that of a scaling object of known thickness. The resulting scaling function relates the brightness of the digitized image and the equivalent thickness of the displayed tissue. The function serves to calculate the quantitative measure of the postirradiation reaction in the tissue. The measure compares favourably with a qualitative scale conventionally used to assess the lung radiation injury. The method appears to be relatively insensitive to variations in conditions of making and digitizing the X-ray images.

1 Introduction

The treatment of neoplasms with a combined method including radiotherapy incurs some risk of toxicity to normal tissues. The knowledge on the processes taking place in such tissue subject to irradiation, possibly undergoing concurrent chemotherapy, is limited.

The postirradiation changes in the normal lung tissue has been chosen as the subject of the present study. For this tissue the relation of the radiation effect to the parameters of the combined modality treatment, such as the total dose, fraction dose, field size, simultaneous administration of chemiotherapeutical drugs, and timing, is still an object of studies (cf. [5] with references). To analyse the influence of these factors, it would be profitable to have a sufficiently sensitive method of estimating the postirradiation changes in the lung tissue.

The normal lung tissue in the narrow safety margin layer around the tumour, which is irradiated during a typical treatment, has been investigated.

It is a typical procedure to estimate the postirradiation reaction on the basis of the X-ray images. The X-ray film density reflects both the thickness and the absorption coefficient of the imaged body. The influences of these two factors can not be separated. In [2] it has been proposed to treat the density of the film as an analog of a single factor – the *equivalent absorber thickness* (EAT). The authors of [2] claim that the changes of this thickness can be treated as a result of the changes taking place in the irradiated site. Actually, the late radiation-induced lung injury is mainly the lung tissue fibrosis, i.e., built-up of fibrin. Also the immediate irradiation related symptom – pneumonitis – can be detected by the thickness-related measure (cf. Fig. 5 A.1 in Section 5). In this way, the equivalent absorber thickness can provide a quantitative measure of the postirradiation reaction in the lung tissue. We have followed that line of reasoning.

In the paper we present a methodology of measuring the EAT of a tissue on the basis of X-ray films digitized with a CCD camera. The X-rays are routinely taken before the start of the treatment and during the post-treatment follow-up of patients.

The presented results have been chosen from those obtained for a group of 13 patients with the limited disease small-cell lung cancer treated with combined modality therapy at the Center of Oncology, Warsaw, between May 5, 1991 and March 1, 1993. Comprehensive information on the treatment and the full documentation of the study can be found in [3]. A total number of 109 X-ray images were analysed. Here, the method is exemplified with the results obtained for two patients.

The measurements have served us as a basis for finding the quantitative measure of the postirradiation reaction in the normal lung tissue in the patients. The found quantitative measure has been compared with the qualitative measure according to the scale of Overgaard [6]. This qualitative measure has been chosen from among other scoring systems (cf. [4, 1]), as it is conventionally used in lung radiotherapy at the Center of Oncology.

There is still a number of questionable points in the methodology we used. Nevertheless, the comparisons we made indicate that the quantitative measure and the qualitative one are in good correlation. Moreover – and this seems to be very promising – the quantitative measure can provide more detailed insight into the dynamics of the ongoing postirradiation process.

The method comprises experimental scaling of the measuring system to compensate for the nonlinearities inherent in the X-ray technique. Scaling should be done each time the conditions of taking the X-ray image are changed. If it can be assumed that these conditions have been relatively constant, also retrospective studies based on plenteous collections of treatment documentation stored at numerous sites are possible.

2 Overview of the method

The postirradiation reaction in the patients has been investigated with the use of the quantitative measure calculated on the basis of digitized X-ray images. The measure, described in detail in Section 4 (Eqs. (2), (1)), is based on a comparison of the EAT of the lung tissue in the given, irradiated region on the X-ray at a given time, to the EAT in the same region at the time before the irradiation. At each time, the EAT in the irradiated region is related to te EAT in a reference region, which for a given patient is fixed for all the films. The reference region has been chosen in the lung opposite to the irradiated one. Due to a movement of the tissues around the tumour together with its contraction, which is an effect of the therapy, the region of the irradiated normal tissue has had to be properly moved towards the vanishing tumour in subsequent X-ray images. In all the cases the regions were $16*40$ pixels large, which corresponds to about $1*2.3$ cm in the patient. An example of the position of the regions can be seen in Fig. 4, Section 5. We have tried, as far as it was possible, to avoid including bones in the regions.

The X-ray images have been digitized with a CCD camera with a frame grabber which provided for resolution of $512*512$ pixels and 256 levels of grey. The area of the image of lungs was fitted into the field of view with a zoom lens. A negatoscope which back-lighted the films was 190 cm away from the camera. Geometrical distortions of the images could be neglected not only because the distance was large, but also because in our application they were not important. A slight unevenness of lighting was also neglected at this stage.

The grey level in a digitized image is related to the density of the X-ray film, but it is not this relation we are interested in. In fact, we seek for the relation between the grey level of a pixel in the digitized image and the EAT – *equivalent absorber thickness* – of the corresponding small region of the lung. This relation is inevitably nonlinear. The measuring chain starting from the X-ray apparatus and ending at the frame-grabber image memory is long. It depends on a large number of factors, such as the settings of the X-ray apparatus, the parameters of the used film and its development, the light conditions of taking the image with the CCD camera, and the settings of the lens and the frame grabber. Facing the abundance of uncertainty concerning these factors and the way they influence the relation we want to find, we have chosen scale the measuring system experimentally.

In the scaling of the measuring system we have tried to find a direct relation between the grey level of the digitized radiograph of an object and its known physical thickness. This relation will be referred to as the *scaling function*. The details are described in Section 3.

The scaling function found can be used to transform the intensity of the digitized X-ray image of a lung tissue into the thickness of an equivalent layer of an aluminium absorber. Therefore, the calculated EAT is the thickness related to aluminium.

3 Scaling of the measuring system

A direct relation between the thickness of a known object and the grey level of its digitized X-ray image can be found, if the thickness of this object is known at each point. This object will be called the *scaling object.* We have used a stepped aluminium phantom, frequently used in testing the X-ray apparata. Its thickness changes in 11 steps, 3.17 mm each, from 3.17 to 34.87 mm.

It can be argued that the attenuation of the Röntgen rays in aluminium is different from that in a human tissue. Actually, we agree that the phantom we have used was not the best choice, also because of another reason which will be described below. However, at the beginning of the study we did not have a better scaling object.

An X-ray of the scaling object is made, developed and digitized with a CCD camera in the same conditions as those used when making the X-rays of lungs of a patient. The thickness $H(P_k) = H_k$ of the object at a small region which corresponds to a pixel $P_k, k = 1, \ldots, K$, in the digital image is known, as well as the image intensity $I(P_k) = I_k$ at P_k. Thus, for each P_k we have I_k and H_k, and these two values correspond to each other.

The image of the scaling object is discrete, and the number of pixels K is limited, so the set of values I_k is limited, as well as is the set of H_k. Let us sort I_k in an ascending order, obtaining a series $\mathcal{I}_l, l = 1, \ldots, K$. From the physics of the phenomenon we know that

$$\forall_{k_1,k_2} \;\; H_{k_1} > H_{k_2} \Leftrightarrow I_{k_1} > I_{k_2}$$

hence, a series $\mathcal{H}_l, l = 1, \ldots K$, of the values H_l corresponding to I_l, will also be sorted in an ascending order. The pairs $(\mathcal{H}_l, \mathcal{I}_l), l = 1, \ldots, K$ can be used as interpolation nodes for recovering the sought scaling function $H(I)$.

In the described experiment, an image of the scaling object has been made and one line has been chosen in it (Fig. 1). The thickness of the object along this line is a stepwise function, with 12 steps[3]. As the nodes of interpolation $\mathcal{I}_l, l = 1, \ldots, 12$, the midpoints of the steps have been taken. The corresponding values $\mathcal{H}_l$ are known. The plot of the intensity function $I(c)$ along the chosen line (across the subsequent columns c) is shown in Fig. 2. The function is noisy; therefore, as each $\mathcal{I}_l$ the mean of a number of values of $I(c)$ around the corresponding node has been taken.

The equivalent absorber thickness EAT, in relation to aluminium, is the thickness of the phantom H. It is expressed in the same units in which H has been measured. However, due to the dimensionless form of the expression in which EAT will be used (formula (2) in Section 4), these units are of no importance.

In the present work it has been decided to store the images in a form transformed from brightness to EAT. Therefore, EAT has been expressed in arbitrary units chosen so as to utilize the whole range of possible values, that is, $\langle 0, 255 \rangle$.

Let us note that the value of the scaling function $H(I)$ is an integer, as well as its argument. This makes it possible to express $H(I)$ as a look-up table,

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[3] 11 steps of the phantom, and zero thickness beyond the phantom.

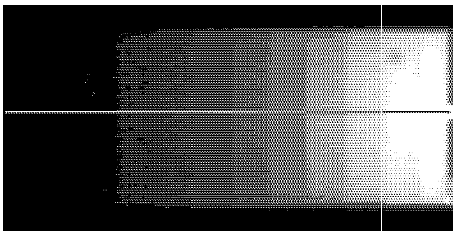
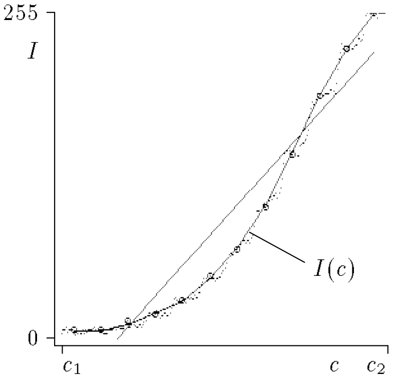


Fig. 1. X-ray of the scaling phantom (125 KV, film: AGFA). The line in which image intensity has been measured (Fig. 2) is marked.

which greatly improves the operation of transforming the brightness image into a thickness one. The scaling function found from the plot of Fig. 2, represented as a LUT, is plotted in Fig. 3.



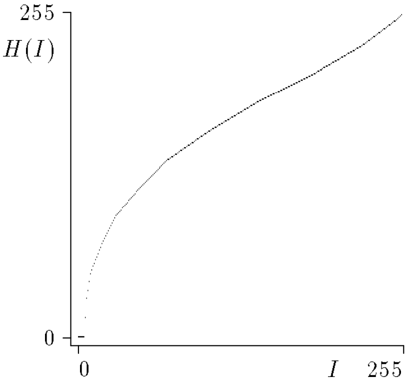


Fig. 2. Intensity function in the line marked in Fig. 1. Stepwise, noisy plot corresponds to stepwise thickness of the phantom. $I(c)$ is interpolated between nodes (circles). c: column of the image ($c \in \langle c_1, c_2 \rangle$). A LSQ fitted straight line shown for comparison.

Fig. 3. Scaling function $H(I)$ found from the function $I(c)$ from Fig. 2, represented as a LUT. H is equivalent to EAT related to aluminium.

A scaling function found for given settings of the measuring system can be applied to recover information from the images made with the same settings. However, in the case of this pilot study we have encountered some difficulties. We have had the radiographs made in the past, and the image of the scaling object made at present. This image has been made in typical conditions, such as those in which the remaining radiographs should have been done. However, it became apparent that the X-rays of the lungs differed between each other, and in general were significantly brighter than that of the phantom. In other words, the thickness of the phantom appeared to be too small for the application to lungs radiographs.

What we could do was to digitize the radiograph of the phantom with "more light" than it was in the case of all the lungs radiograms. Actually, we have tried to make both the images of lungs and the phantom in a way to utilize the full range of grey levels available in our frame grabber. The settings used in digitizing the phantom image were: lens diaphragm F11, frame grabber reference levels: $2, 174$[4], and for the lungs: diaphragm F16, levels: $2, 158$.

In fact, we consider this difference in light conditions of digitizing the images as the most questionable point of the present study. A better suited scaling object is in use in the new series of measurements which are now under way. Additionally, this new object is made of a substance which is a good model of the lung tissue with respect to interaction with the Röntgen rays. However, the positive results obtained in the first experiment encouraged us to present them in the original form[5].

4 Quantitative measure of the postirradiation reaction

4.1 The measure used in the experiments

In the experiments described in this paper the measure introduced in [2] has been used. It is constructed as follows. Let us denote

$$\Delta(t) = [EAT_I(t) - EAT_R(t)] - [EAT_I(0) - EAT_R(0)] \tag{1}$$

where:

$EAT_X(0)$ – equivalent thickness in the region X before the treatment;
$EAT_X(t)$ – equivalent thickness in X at time t after the treatment;
X – region: I: Irradiated; R: Reference.

The thickness in the reference region $EAT_R(.)$ has been introduced to compensate for such factors as the change of the patient's weight, or the darkening of the film with time.

The relative measure of the radiation effect which renders Eq. (1) independent of the units of EAT is

$$\tilde{\Delta}(t) = \frac{\Delta(t)}{EAT_I(0)} \tag{2}$$

As the thickness EAT of the given region, the mean thickness in the pixels of that region has been taken.

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[4] Upper and lower reference levels in the frame grabber, i.e., comparative voltages for the A/D converter, are chosen within the interval $\langle 0, 255\rangle$.

[5] Limited place restricts us from presenting the comparison of results obtained with the scaled images and with the ones without scaling, but it is evident that scaling, even in the preliminary form presented here, is a step in the right direction (see [3]).

4.2 Invariance of the measures

According to [2], the relative character of the measure $\tilde{\Delta}$ (2) should provide for its insensitivity to other factors than the radiation injury, which is of main interest.

In Eq. (1), an arbitrary component $b(t)$ can be added to each $EAT_X(t), X = I$ or R, which does not change the value of Δ ($b(t)$ can be different for each time t). The measure $\tilde{\Delta}$ according to (2) does not have this feature, due to the presence of the denominator. However, this denominator is the same for each time t, so its changes lead mainly to scaling all the results, without significantly changing their mutual relations[6].

On the basis of the equivalent absorber thickness EAT a number of other quantitative measures of postirradiation reaction can be postulated. We can take for example:

$$\begin{aligned}\tilde{\Delta}_1(t) &= \frac{[EAT_I(t) - EAT_R(t)] - [EAT_I(0) - EAT_R(0)]}{EAT_I(0) - EAT_R(0)} \\ &= \frac{EAT_I(t) - EAT_R(t)}{EAT_I(0) - EAT_R(0)} - 1 \end{aligned} \tag{3}$$

This formula provides for invariantness not only with respect to addition, but also to affine transformations of the form $a * EAT + b(t)$ (the components $b(t)$ can be different, but the factor a must be the same for each time t). Hence, the formula compensates the displacement along the characteristic curve of an X-ray film, but not for the differences in the tilt of this curve for various films.

The formula has another drawback. In [2] it is recommended to place the reference region symmetrically to the irradiated region. Here, this requirement should have been relieved, as the denominator could become near or equal to zero.

For better stability of the results, the formula (3) can be modified by introducing a larger number of reference areas:

$$\tilde{\Delta}_2(t) = \frac{EAT_I(t) - \frac{1}{2}[EAT_{R_1}(t) + EAT_{R_2}(t)]}{EAT_I(0) - \frac{1}{2}[EAT_{R_1}(0) + EAT_{R_2}(0)]} - 1 \tag{4}$$

where R_1, R_2 – two reference areas. However, the necessity of choosing an additional reference area will increase the arbitrariness of the measuring procedure.

To obtain the invariance of the radiation effect measure to the tilt of the characteristic curve of the X-ray film, i.e., the invariance to multiplication, a following measure δ_1 of the thickness of the irradiated region related to the reference region, at the time t, can be introduced:

$$\delta_1(t) = \frac{EAT_I(t) - EAT_R(t)}{EAT_R(t)} \tag{5}$$

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[6] This is the reason why the maximum values of the measure (2) are different for different cases, cf. Fig. 5 in Section 5.

The quantity $\delta_1(t)$ is invariant to multiplication of EAT by an arbitrary factor. As a measure of radiation effect, each of the following two formulae can be chosen:

$$\tilde{\Delta}_3(t) = \delta_1(t) - \delta_1(0) \tag{6}$$

$$\tilde{\Delta}_4(t) = \delta_1(t)/\delta_1(0) \tag{7}$$

To obtain the invariance to multiplication as well as to addition, two reference regions: R_1 and R_2, can be used:

$$\delta_2(t) = \frac{EAT_I(t) - EAT_{R_1}(t)}{EAT_{R_2}(t) - EAT_{R_1}(t)} \tag{8}$$

and two measures of the radiation effect can be introduced, similarly as in (6) and (7):

$$\tilde{\Delta}_5(t) = \delta_2(t) - \delta_2(0) \tag{9}$$

$$\tilde{\Delta}_6(t) = \delta_2(t)/\delta_2(0) \tag{10}$$

It is clear then that there is a large degree of arbitrariness in choosing the quantitative measure of the postirradiation reaction. The choice of formulae (1), (2) for the present study resulted from the desire to have a possibility to compare the results obtained with those to be published by other authors. Which measure will be accepted in further investigations remains an open question.

5 Results of the experiments

From a number of results carried out, two series obtained for two patients have been chosen for this presentation. For these two patients the quantitative measure of the postirradiation reaction have been calculated and compared with the qualitative measure, according to the scale of Overgaard [6].

The series have been assigned symbols OT and SR. One of the images of lungs, transformed to the scale of the equivalent thickness (scaled), belonging to the series OT, is shown in Fig. 4. The two regions: the irradiated and the reference one, are marked in this Figure (see Eqs. (1-2), Section 4).

The graphs of the quantitative and the qualitative measures obtained have been compared in Fig. 5, A and B. The conformity of the results obtained with the two different methods of estimating the postirradiation reaction is apparent in both presented results.

The quantitative measure, being a real number, reflects the dynamics of the process in a more precise way. For example, the state in the case OT between the month 15 and 23 seems to be stable as far as the qualitative measure is considered (Fig. 5, A.2), while the quantitative measure (A.1) reveals some growing tendency. In the case SR (Fig. 5, B.1) it can be seen that the growth of the reaction between months 2 and 9 is a continuous process, whereas the graph of the qualitative measure (B.2) has steps. It should be stressed that this result

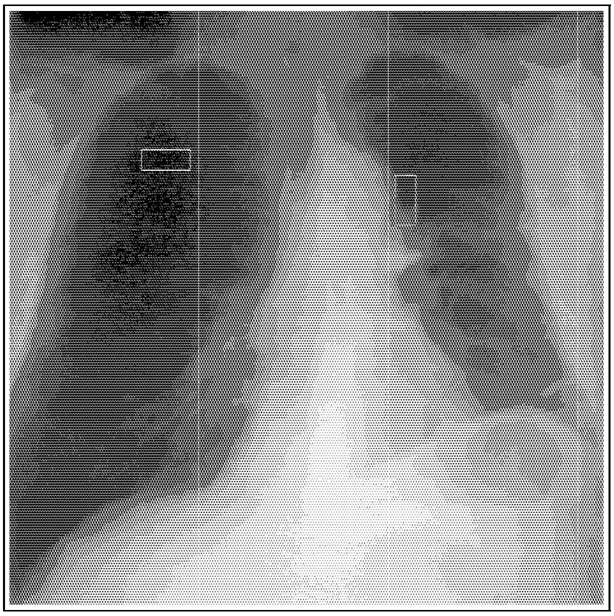


Fig. 4. X-ray no. 8 in the series OT (after approx. 16 months after the treatment) with the regions marked: irradiated – left lung and reference – right lung.

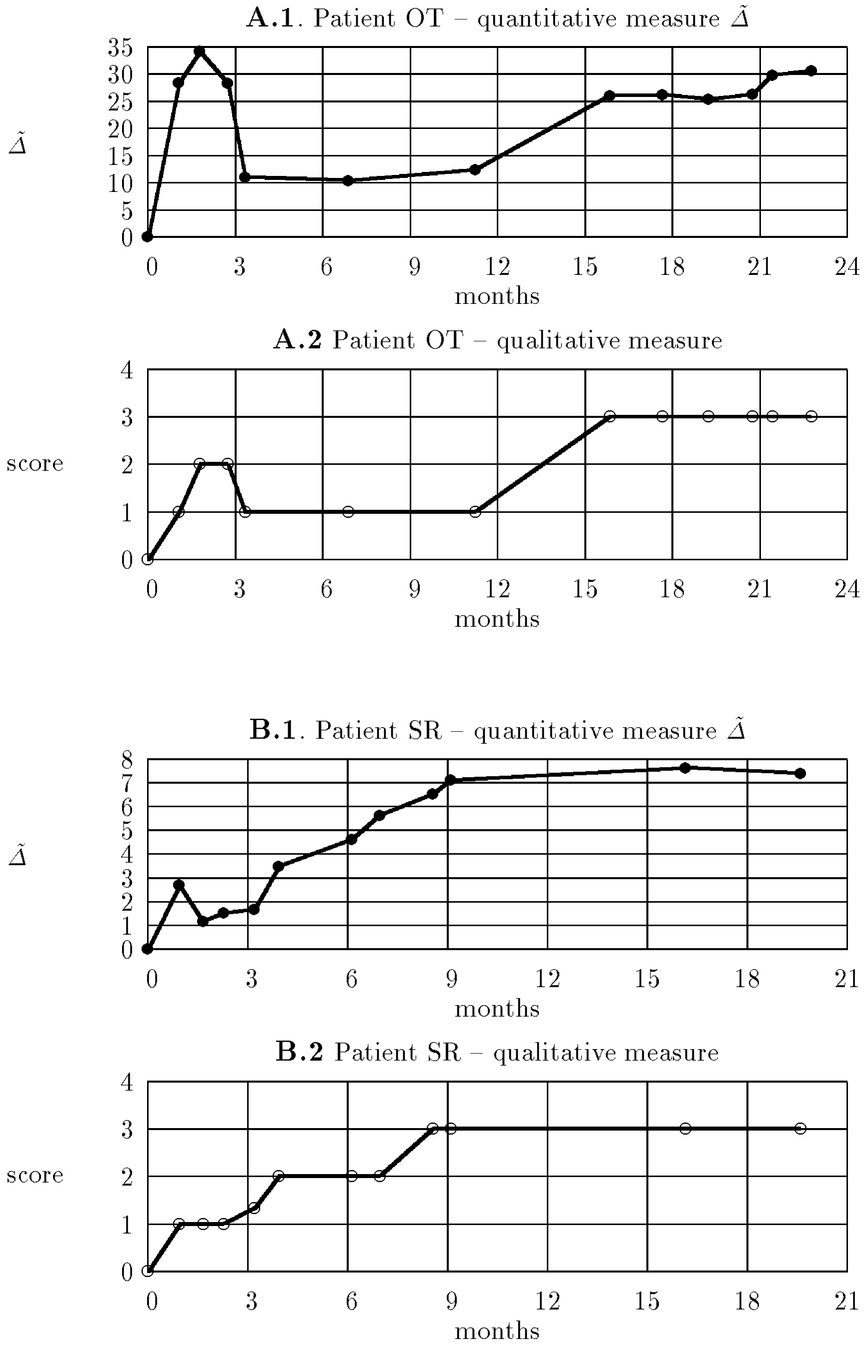
of the limited number of its possible values can not be overcome by any scoring system based on examination of images by a human eye, because the accuracy of such scoring is inevitably limited.

Let us remind one more time that the condition of uniformness of the parameters of taking and digitizing the X-ray images of the tested tissues and of the scaling object was not strictly fulfilled. In spite of that, the described method leads to satisfactory results, which means that its application in practice could be considered.

6 Conclusion

A quantitative measure of the postirradiation reaction in the normal lung tissue has been investigated. This measure, based on the concept of the *equivalent absorber thickness* (EAT), has been estimated on the basis of the series of the X-ray images of lungs, made just before the treatment of cancer and in the follow-up period afterwards.

The method of estimating the EAT from the X-ray images has been proposed. It consists in comparing the digitized image of the radiograph of the tested tissue with that of a scaling object of known thickness. From this comparison a *scaling function* which expresses the relation of the brightness of the digital image of the tissue radiograph and the equivalent thickness of the tissue displayed in this image can be easily found. The scaling function can be used to recover the lung



A.1. Patient OT – quantitative measure $\tilde{\Delta}$

A.2 Patient OT – qualitative measure

B.1. Patient SR – quantitative measure $\tilde{\Delta}$

B.2 Patient SR – qualitative measure

Fig. 5. Comparison of the measures of postirradiation reaction for two patients.

tissue thickness, and consequently, to calculate the measure of the postirradiation reaction in this tissue, from the X-ray images made in the same conditions as those in which the image of the scaling object has been made.

The comparison of the quantitative measure found with the method proposed in this paper with the conventional scoring scale based on qualitative assessment of X-ray images indicates the conformity of these two measures of postirradiation reaction. Moreover, the results seem to favour the quantitative measure over the qualitative one in that it gives a more precise image of the dynamics of the postirradiation process.

The above described optimistic results are not greatly impaired by the fact that the stability assumption which concerns the conditions of making and digitizing the radiographs was not strictly fulfilled. This makes it possible to consider the application of the proposed method to evaluate the X-ray images stored in documentation bases of numerous medical institutions, in order to study the relation of the radiation effect in the normal lung tissue to the parameters of the combined modality treatment of cancer.

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