Uncertainty Estimation Method for Determining Bone Density in Patients with Infiltrating Intraductal Carcinoma Undergoing Anti-Cancer Therapy

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Abstract

Identification of a bone density is crucial in all branches of medicine. Assessing bone density is a labor-intensive process. Bone density is quite unstable and depends on many factors, both physiological (aging, hormonal balance) and pathological (medication use, various underlying conditions).

The aim of our study is to determine bone density in patients with malignant breast tumors undergoing anti-cancer therapy.

Material and Methods. The study included 50 women aged 60-70 years who were diagnosed with infiltrating intraductal carcinoma. According to established protocols, MSCT is recommended for this category of women at intervals of once every six months. The first MSCT scan was performed immediately after the diagnosis was made, before the start of treatment, and the second scan was conducted six months later.

Results. The maximum radiological density was 75.8954±37.9477 Hu in the group of women who had been receiving treatment for six months, compared to 93.9388±46.9694 Hu in the group of patients who did not take the drug. Meanwhile, the minimum density showed a slight increase from 29.7295±14.8647 Hu to 38.6919±19.3460 Hu, which can be attributed to the compensatory mechanisms of the body.

Conclusions. In the course of this study, bone density in patients with infiltrating intraductal carcinoma undergoing anti-cancer therapy was determined using uncertainty estimation. It was found that after six months, the first to respond to changes in density was the maximum bone density.

Keywords

Infiltrarive intraductal adenocarcinoma, multislice computer tomography , radiological bone density

1. Background

Identification of a bone density is crucial in all branches of medicine. Assessing bone density is a labor-intensive process [1, 2]. Bone density is quite unstable and depends on many factors, both physiological (aging, hormonal balance) [5] and pathological (medication use, various underlying conditions) [6]. The difficulty in determining bone density is due to its structure. Currently, data on bone density primarily concern long bones, determined using dual-energy X-ray absorptiometry (DEXA) [7], which requires additional time and personnel, making it economically unfeasible despite being the gold standard for osteoporosis diagnosis. Assessing trabecular bone density poses significant challenges due to its spongy structure and numerous intertrabecular spaces. Multislice computed tomography (MSCT) is one method used to determine bone density [8]. One of the simplest methods for measuring bone density is the radiological method (often computed tomography, less frequently magnetic resonance imaging). Radiological research methods can accurately and effectively determine the bone density of any area of the human skull in both physiological and

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pathological conditions [9]. However, the majorities of studies focus on the physiological state or investigate radiological density in the presence of tooth and jaw pathology, particularly the alveolar process of the upper jaw.

To explore the biological mechanisms underlying changes in bone density, especially the compensatory mechanisms that might lead to an increase in minimum density, you could focus on several key areas such as bone remodeling process, Wolf law, homeostasis of microelements, hormones, genetic faktors. An increase in minimum density may suggest that osteoblast activity is heightened or more efficient, possibly as a compensatory mechanism in response to earlier bone loss or mechanical stress.

One of the advanced methods for calculating density could be the use of uncertainty estimation. Measurement uncertainty is a characteristic of inaccuracy of measurements, adopted at the international level [10], which is associated with the measurement result and characterizes the range of values that can reasonably be attributed to the measured value.

Using MSCT and uncertainty estimation, it is possible to determine bone density not only under physiological conditions but also in the presence of pathological processes, one of which is breast cancer. This disease is the most common type of cancer among women in 157 out of 185 countries worldwide [11, 12].

The progress in our framework of knowledge is pushing breast cancer (BC) treatment forward, while new details widen its inner diversity and at the same time they solidify our views at the consistency between carcinoma's features and approaches to its management. Considering sensitivity of many BC subtypes to sex steroid hormones (SSH) the maintenance of disruption of the pathways that keeps afloat communication between tumour cells and these agents is viewed as the pivotal issue of recurrences prevention [13]. From the other hand, deprivation of a woman under 50 years old from estrogen's beneficial influence does affect adversely her body in different aspects. Of course, to rescue the life from such insidious foe as BC is worth that and it is not the question to discuss itself, but to explore how deep and fast the fallouts of these interventions is very important in order to clarify when new perils would emerge at the extent of the true jeopardy to the quality of life. Age under 50 yo and luminal A breast cancer requires use of gonadotropin-releasing-hormone agonists (aGnRH). When the bone tissue is exposed to the profound estrogen deficiency it is getting devoid of what constitutes bone density due to the preponderance of constructive work over destructive processes. Unfortunately, there is no chance to counteract by the use of hormonal replacement therapy whereas bisphosphonates aren't able to bridge all the gaps [14].

Given all of the above, **the aim of our study** is to determine bone density in patients with malignant breast tumors undergoing anti-cancer therapy.

2. Material and Methods

The study included 50 women aged 60-70 years who were diagnosed with infiltrating intraductal carcinoma. According to established protocols, MSCT is recommended for this category of women at intervals of once every six months. The first MSCT scan was performed immediately after the diagnosis was made, before the start of treatment, and the second scan was conducted six months later. Our study put under scrutiny the pace of the bone density loss driven by aGnRH use in women under 50 yo passing through their BC treatment (diphereline 22.5 mg 6 months alone and combined with tamoxifen).

To determine the short-term effects of Diphereline, we conducted a study six months after the initiation of treatment with Diphereline. Bone density was measured in the region of the first cervical vertebra, specifically in the part of the vertebra closest to the spinal canal. The maximum and minimum bone densities were calculated separately.

The study was approved by the bioethics committee of Kharkiv National Medical University (protocol No. 1 dated 08.11.2018).

The research was conducted at the Clinical Institute of Emergency Surgery, Kharkiv, based on the existing collaboration agreement between this medical institution and Kharkiv National Medical

University. CT scans were performed on a Toshiba Aquilion-64 spiral computed tomography scanner. The Toshiba Aquilion 64 CT machine is considered the only true volumetric 64-slice CT scanner with 64 detector channels, 3-D cone beam algorithms and volume reconstruction on the market. Automated features in the Toshiba Aquilion 64 CT scanner's SUREWorkflow software enable the operator to monitor a patient's heart rate prior to scanning.

Toshiba's 3-D Quantum denoising allows for reducing patient radiation exposure by up to 40% without loss of image quality. Each Toshiba Aquilion 64 CT scanner also features volume reconstruction, enabling you to scan a large volume in a minimum of time as Volume Viewing automatically reconstructs scanned data into the isotropic volume used for diagnosis [15].

Preference was given to multislice computed tomography (MSCT) due to its simplicity and the ability to determine density during this investigation. Density calculations were based on the Hounsfield scale – a scale of gray shades widely used in MSCT. This scale is relative, with water (density assumed as 0 HU) and air (-1000 HU) as benchmark values. Each organ and tissue has its characteristic density value, and in the presence of pathological processes, radiological density may decrease (more rarely, increase). The obtained images were examined using the RadiANT DiCOM Viewer program [15].

All inputs of uncertainty form a standard uncertainty. To calculate the standard uncertainty, we used the formula:

$$u_c(H_H) = \sqrt{u_A^2(H_{Hi}) + u_B^2(H_{Hi})} \quad (1,$$

where *uA(HHi)* is a standard type A uncertainty, a *uB(HHi)* is a standard type B uncertainty.

Standard type A uncertainty was calculated using the formula:

$$u(H_{Hi}) = \sqrt{\frac{1}{n(n-1)}\sum_{i=1}^{n}(H_{Hi} - H_H)^2} \quad (2)$$

where H_{Hi} – i-th value of the sample measurements, H_H is the mathematical expectation, n is the number of measurements in the sample.

Standard type B uncertainty was calculated using the formula:

$$u(H_H) = H_H \frac{\delta_H}{\sqrt{3}\cdot 100} \quad (3)$$

where δ_H is a measurement error of software not exceeding 0.0001.

After calculating these values, an interval estimation of uncertainty was calculated, namely extended uncertainty U according to the formula:

$$U = ku_c \quad (4)$$

where k is the coverage ratio.

3. Results and discussions

The results of measurements taking into account the expanded uncertainty U are given in the tables 1 and 2. Assessing the data in the table, we can conclude that the probabilistic spread of U value is in the ±U range relative to the measured u_c value, and the degree of certainty for U values in this interval is determined by the probability (confidence level) p = 0.95. Calculation of uncertainty is a quite rarely used method in medicine [16], and is more commonly used in laboratory diagnosis. According to the literature analysis there are no research papers describing proposed approach.

Group 1 includes the subjects who underwent MSCT immediately after the diagnosis, before the administration of Diphereline. Group 2 includes the same women who underwent CT (MSCT) six months after the administration of Diphereline.

As can be seen from Table 1, under the influence of diphereline, the maximum bone density decreases and is 75.8954±37.9477 Hu, at the first CT measurement, this indicator was 93.9388±46.9694 Hu

Table 1
The maximum radiological bone density in 2 groups

Indicator	Group 1	Group 2
U_A (X)	46,969	37,948
U_B (X)	0,00053772	0,00068470
Us (X)	46,9694	37,9477
U(X)	93,9388	75,8954

Table 2
The minimum radiological bone density in 2 groups

Indicator	Group 1	Group 2
U_A (X)	14,8647	19,3460
U_B (X)	0,00003424	0,00001889
Us (X)	14,8647	19,3460
U(X)	29,7295	38,6919

The results of determining the minimum bone density in this group of women were quite unexpected. First, it's important to note that in both groups, the minimum density is relatively low, which may be attributed to the age of the women and hormonal changes associated with menopause. However, after six months of Diphereline treatment, the follow-up MSCT revealed a slight increase in minimum density, which rose from 29.7295±14.8647 Hu to 38.6919±19.3460 Hu (see Fig. 1 and 2). It can be hypothesized that the maximum bone density is the first to respond to Diphereline, which may have more favorable prognostic implications regarding the development of complications. The use of bisphosphonates appears to be justified six months after the start of treatment to maintain maximum bone density at an adequate level.

As for the increase in minimum density, it is likely not directly related to the drug itself; otherwise, we would observe a similar trend in maximum density as well. These changes in density may be due to the compensatory mechanisms of the body.

It is well-known fact that even short streak (<6 months) leaves the evident signs of the bone density decline that takes years to repair [13] let alone the 2-year duration. Of course there are individual swings stipulated by personal background but all of them are more or less subject to some mean pattern. SCT taken as the follow-up after the beginning of the treatment also allows tracing individual bone density decline captured by scan.

By the use of proposed approach that includes assessment of bone density by MSCT as the scheduled follow-up (every 6 month) we obtain the mean curve of the decline inherent mainly for these patients. It turned out that despite quite significant drop of bone density within first 6 months it is rather sluggish comparatively with the next year when the curve of decline slides steeply down. Perhaps this slump is driven by the exhaustion of the resource stocks.

Proposed approach of bone density assessment by the same MSCT within conventional follow-up schedule in the case of being implemented into standard management lets trace a patient's bone density decline in comparison with the calculated mean decline's curve and, if it lowers deeper than expected, may justify the expedience to reconsider the management in favour of earlier intervention with this regard.

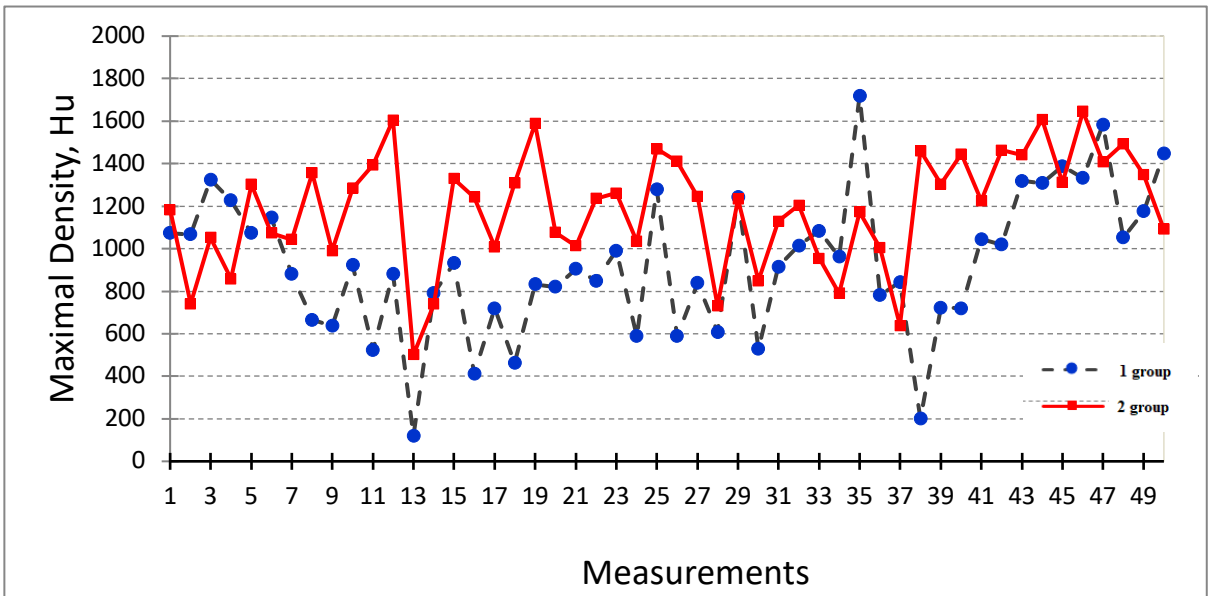

Figure 1: Maximal bone density in 2 groups of patients

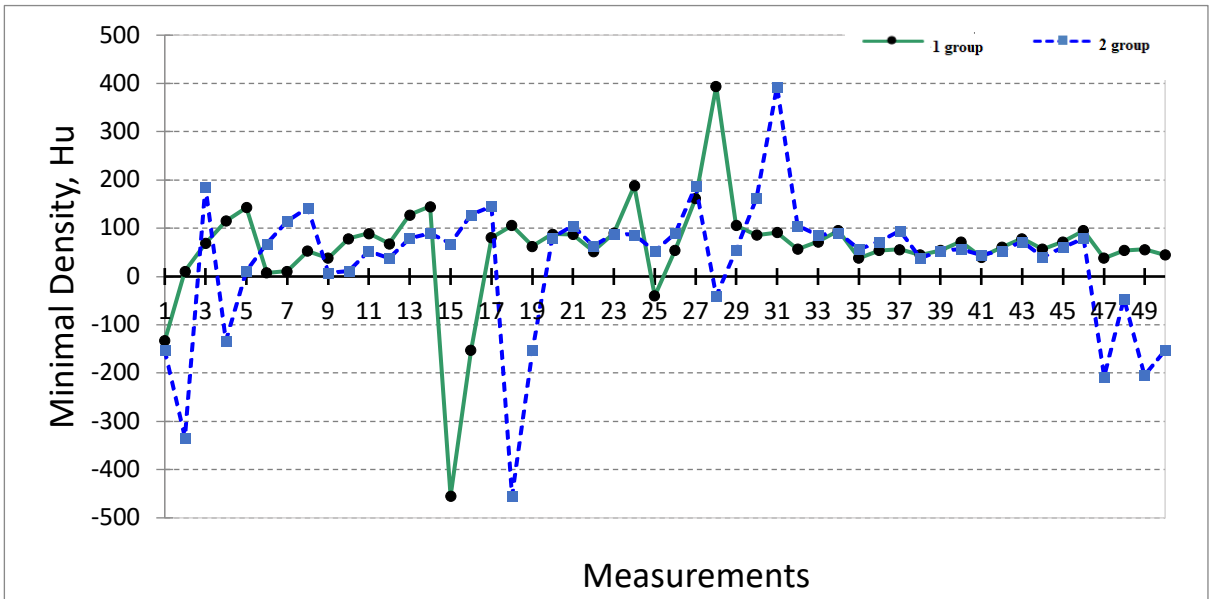

Figure 2: Minimal bone density in 2 groups of patients

Within the scope of investigating how diphereline affects bone density, our findings are consistent with the broader research in the field of healthcare-related intelligent systems. Previous studies on intelligent expert systems for evaluating medical staff knowledge about infections associated with medical care [14, 15], along with research on smart systems, data-driven healthcare services, and the use of smart technologies in medical services, contribute to the expanding knowledge in bone density detection [16-19]. The integration of smart systems and data-driven approaches in healthcare, as discussed by several authors [20-22], highlights the critical role of technology in enhancing medical outcomes.

4. Conclusions

In the course of this study, bone density in patients with infiltrating intraductal carcinoma undergoing anti-cancer therapy was determined using uncertainty estimation. It was found that after six months, the first to respond to changes in density was the maximum bone density. The maximum radiological density was 75.8954±37.9477 Hu in the group of women who had been receiving treatment for six months, compared to 93.9388±46.9694 Hu in the group of patients who did not take the drug. Meanwhile, the minimum density showed a slight increase from 29.7295±14.8647 Hu to 38.6919±19.3460 Hu, which can be attributed to the compensatory mechanisms of the body.

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