Measurement 92 (2016) 89–95

Contents lists available at ScienceDirect

Measurement

journal homepage: www.elsevier.com/locate/measurement

Measurement method for the objective and early detection of the osteosarcoma tumors

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ARTICLE INFO

Article history:
Received 29 October 2014
Received in revised form 3 June 2016
Accepted 7 June 2016
Available online 7 June 2016

Keywords:
Characterization
Thermal analysis
SEM–EDAX analysis
Measurement methods
Osteosarcoma
Cancer
Tumor

ABSTRACT

This paper deals with the characterization, by means of measurement techniques typically used for ceramics and polymeric materials, of human bone samples affected by two aggressive tumors: osteolitic osteosarcoma and sclerotic osteosarcoma. These two common forms of osteosarcoma often affects children and young teenagers. To distinguish between healthy and diseased bone tissue, the Hydroxyapatite/Collagen ratio and the Hydroxyapatite composition (Calcium/Phosphorus molar ratio) are evaluated. The results allow two considerations to be drawn on the analysis of human bone samples. The first consideration is that the bone affected by osteosarcoma has a greater amount of Collagen with respect to the healthy one. This can be used to evaluate the pathologic status of bone tissues. The second consideration is that the Calcium/Phosphorus molar ratio is, with respect to the one of healthy bone, higher in bone tissue affected by osteolitic osteosarcoma, while is lower in the one affected by sclerotic osteosarcoma. On the basis of these considerations, a promising measurement method is proposed to support the early and objective detection of the osteosarcoma tumor and to distinguish between osteolitic and sclerotic forms. The proposed measurement method can be executed in a few minutes and by using few milligrams of bone tissue that can be drawn with a needle under local anesthesia.

1. Introduction

Osteosarcoma is a malignant neoplasm of the bone. It is one of the most common malignant tumors of the bone in both children and adults. It is the third most common malignancy in children and adolescents [1–6]. The World Health Organization subdivides the histologic appearance of osteosarcoma into central and surface tumors, and recognizes a number of subtypes within each group [7]. Osteosarcoma frequently originate in the metaphysis of the proximal humerus, proximal tibia and distal femur. Osteosarcomas are subdivided into the classic forms (75%) and osteosarcoma variants (25%) [8–10]. The variants are a heterogeneous group of osteosarcomas with a range of different imaging and behavioral features. Owing to their wide prevalence, in this paper the classic forms are considered [11].

The classic osteosarcoma grows in a radial manner, which invades the bony cortex forming a ball-like area of new bone formation/destruction that compresses the surrounding soft tissues/-muscles effectively forming a pseudo capsule termed as the "reactive zone". Satellite nodules invade the reactive zone. To ensure effective surgical therapy the entire abnormal bone including the reactive zone containing the satellites is resected with wide surgical margins. Osteosarcoma can metastasize regionally or systemically. The presence of metastasis worsens the prognosis dramatically. Tumor nodules that grow outside the reactive zone but within the same bone or across a neighboring joint are called "skip lesions" and represent regional metastases. Lungs are the commonest site of systemic metastases. The skeleton forms the second most common site of metastatic disease but generally it occurs after pulmonary metastases [12]. The classic osteosarcoma includes, osteolitic and sclerotic forms.

Fig. 1 shows radiographs from two different patients depicting a osteolitic lesion of the tibia (a) and a sclerotic lesion of the lower femoral metaphysis (b) [12]. Both lesions proved osteosarcomas on biopsy.

These tumors penetrate and destroy the cortex and trabecular region of the bone and extend into surrounding soft tissues. It arises in bone during periods of rapid growth and primarily affects adolescents and young adults. The 5-year survival rate for osteosarcoma is 60–70% [12]. The early detection of the diagnosis

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http://dx.doi.org/10.1016/j.measurement.2016.06.010
0263-2241/

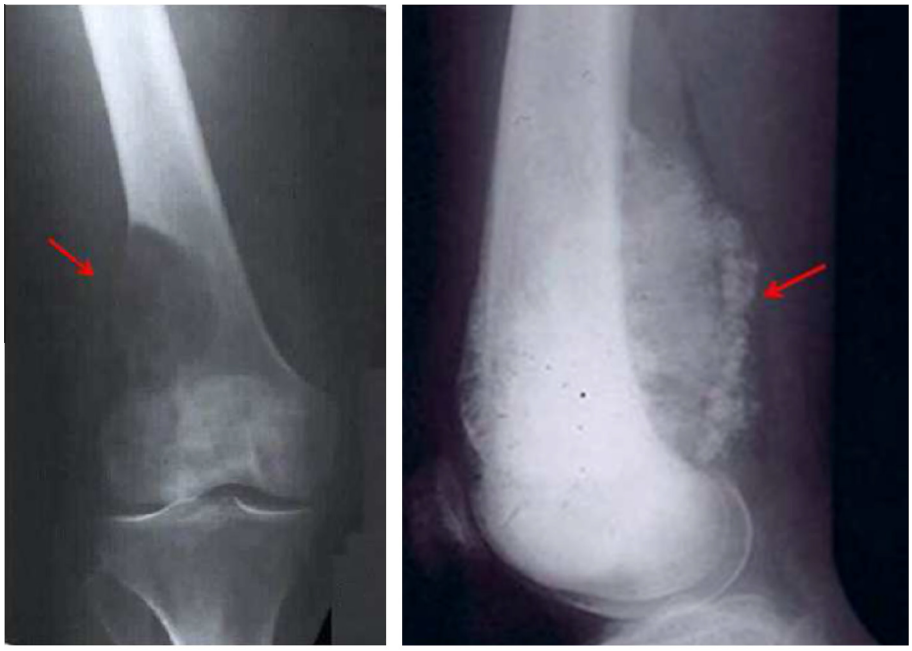

Fig. 1. Osteolitic osteosarcoma (a) and sclerotic osteosarcoma (b) [12].

increases this percentage, owing to its sensitivity to chemotherapy. Up to now, the diagnosis of osteosarcoma remains has focused on the anatomical understanding of the disease, and often it is performed when pulmonary metastasis arises [7]. The need for early and objective detection measurement techniques is highlighted in [13] where it is proposed to improve the prognosis of patients with osteosarcoma through tumor-targeted therapies. Many efforts in the field of measurements were devoted to furnishing methods for the continuous monitoring of health parameters [14], to detect the action of carcinogens [15,16], and to analyze bone tissue [17–23]. In [17] the use of Ultrasound Transmission Velocity (UTV) was proposed to assess osteoporosis in order to overcome the assumption that the thickness of the heel bone is fixed, and to cope with the effects of covering soft tissue. In [18] ultrasounds were proposed to assess bone fragility. In [19–21] the electrochemical impedance spectrum measurement was proposed to assess prosthesis osseointegration, so as in [22] capacitive displacement sensors and resonance frequency (RF) analysis were used to measure and evaluate the severity and location of imperfections surrounding the bone-implant. In [23] echo sound backscattering was proposed for measuring the trabecular bone density. These methods have been proposed as alternative to radiography, where patients and clinicians are exposed to the potential risks of radiation [17].

Nowadays, there are no widely recommended screening tests for this cancer [24]. Symptoms such as bone pain or swelling often prompt a visit to a doctor, and, as a consequence, the level of pain tolerance of the patience and the experience of the doctor are often decisive for the early detection of the osteosarcoma [24]. The following steps are the execution of medical imaging tests as magnetic resonance imaging (MRI) scan, computed tomography (CT) scan, positron emission tomography (PET) scan. These tests require the use of radioactive substances injected into the blood and the sedation of patients owing to the length of execution [24]. In all these cases the correct diagnosis of the disease depends on the ability of the clinicians in reading the medical images. The final step can be the surgical resection of the bone with the goal to remove all the cancer cells. To this aim, surgeons remove the diseased tissue plus some of the normal tissue that surrounds it and a pathologist must look at the removed tissue under a microscope to see if the margins contain cancer cells. If cancer cells are detected, the surgeons must resect further bone tissues. As a consequence, nowadays, the resection point is established on the basis of the pathologist's ability and expertise in the reading of the cell slides [24].

This paper proposes an objective measurement method to help pathologists and clinicians in the diagnosis. Since osteosarcoma alters the regenerative mechanism of the bone, mainly depending on the Collagen and the Hydroxyapatite [25], the detection of changes in the Collagen Hydroxyapatite ratio with respect to that of healthy bone can be considered as an objective indicator of the osteosarcoma action.

Thermal analysis is proposed to measure this ratio because: (i) it does not expose patients and clinicians to the potential risks of radiation; (ii) it can be performed on few milligrams of bone (at least 20 mg), (iii) owing the reduced quantity, the bone sample can be draw by means of a needle in ambulatory under local anesthesia [26,27], or directly in the surgical room; (iv) thermal analysis can be performed in less than 15–20 min; and (v) thermal analysis can be performed directly in the surgical room. Moreover, since thermal analysis is a well-known and routine measurement technique for the study of ceramics and polymeric materials, the measurement instrument is easily available commercially.

For the above reported reasons the proposed measurement method can be considered a promising objective tool to support the diagnosis of the osteosarcoma tumors and then to increase the probability of patient survival, which nowadays mainly depends on the ability and experience of clinicians.

2. Measurement techniques

Bone is formed by a mixture of an organic matrix, principally Collagen with Calcium Phosphate, mainly Hydroxyapatite. In addition, the bone minerals are in the metabolic interrelation with body fluids, serving principally as a reservoir for body minerals,