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● *Original Contribution*

QUANTITATIVE ECHOGRAPHY IN THE FOLLOW-UP OF PATIENTS TREATED WITH PROTON-BEAM IRRADIATION FOR PRIMARY CHOROIDAL MELANOMAS

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Abstract—Quantitative ultrasonic characterization yields information that is correlated to the tissue microstructure and increases the diagnostic potential of ultrasound. The measurement of acoustic properties of melanomas *in vivo* has not yet been reported after proton-beam irradiation. This prospective study was conducted on a cohort of 50 patients diagnosed with primary malignant melanoma to assess *in vivo* the ability of quantitative echography to detect changes in choroidal malignant melanomas after proton-beam irradiation and to follow the ultrasonographic changes during 24 months posttreatment. Echographic evaluations of these patients were performed at diagnosis and repeated every 6 months after treatment over a 2-y period. The acoustic parameters included in this work are derived from the calibrated tissue backscatter spectra (spectral slope, spectral intercept and apparent integrated backscatter) of a selected tumor volume after correction of the apparatus transfer function and beam diffraction. Clinical parameters resulting from conventional echography were also quantified and included mainly tumor height, tumor vascularity and internal reflectivity. Spectral intercept and apparent integrated backscatter were found to be the most useful to evaluate changes in melanomas after treatment. Significant ($p < 0.05$) differences of these parameter values were observed between pre- and postproton therapy. In particular, significant changes (compared with baseline) were observed for these parameters, even when the tumor size after treatment was not significantly different from baseline. The results suggest that quantitative spectrum analysis of frequency-dependent backscatter can provide information about the structural modifications of choroidal malignant melanomas as a result of proton-beam irradiation. (E-mail: michele.boudinet@lip.bhdc.jussieu.fr) © 2007 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Ultrasound, Ultrasonic tissue characterization, Spectrum analysis, Ocular tumor, Choroidal melanoma, Proton-beam irradiation, Frequency-dependent backscatter.**

INTRODUCTION

Malignant choroidal melanoma is the most common primary intraocular tumor in adults. In a majority of cases, these tumors are accessible with conservative treatment, especially by an irradiation modality like proton-beam irradiation or plaque brachytherapy. The advantage of proton-beam radiotherapy is to deliver a uniform dose-irradiation within the tumor volume, with preservation of surrounding tissues (Gragoudas et al. 1987). In most cases, proton-beam therapy of choroidal melanoma allows conservation of the eye (Desjardins et al. 1997) and an overall survival rate of 79% at 5 y (Dendale et al. 2006). New therapeutic approaches are being evaluated for treating ocular melanomas, such as thermal treatment with high-intensity focused ultrasound (Lizzi et al. 1999, 2003) and transpupillary thermotherapy with infrared diode laser for small choroidal melanomas (Shields et al. 2002). However, large tumors are still often managed by enucleation (surgical removal of the eye).

The diagnosis of intraocular tumor with echography was popularized in the 1970s (Coleman 1973) and widely used to monitor the effects of treatment. This probably represents the most powerful examination in terms of reliability and noninvasive nature. Quantitative echography of intraocular tumors was introduced by

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Ossoinig (1974) and was based on criteria derived from an A-mode echogram. Additional information related to ocular tissue structures can be obtained using quantitative analysis of radiofrequency (RF) ultrasonic signals to measure acoustic parameters such as the frequency-dependent attenuation (Lizzi et al. 1976; Lizzi and Coleman 1977; Cloostermans et al. 1985) and backscatter coefficients. Lizzi et al. (1983) described the principles of a method based on calibrated power spectrum analysis for noninvasive evaluation of ocular tissues. Quantitative parameters derived from the backscattered power spectra can be linked, using adequate models, to the mean size and concentration (number per unit volume) of scattering structures in the tissue (Feleppa et al. 1986; Lizzi et al. 1986).

Several studies demonstrated the clinical value of quantitative spectrum analysis for the discrimination of different types of intraocular tumors and its ability to separate spindle cell malignant melanomas from the more lethal mixed or epithelioid melanomas under *in vivo* conditions. These results led to the noninvasive classification of intraocular tumors (Coleman et al. 1983, 1985a). Clinical applications using these techniques were reported aiming at monitoring tumor response to cobalt-60 radiotherapy (Coleman et al. 1985b). A significant variation of ultrasound backscatter was observed after treatment by cobalt-60 plaque and/or hyperthermia (Coleman et al. 1986, 1987; Feleppa et al. 1987, 1988; Silverman et al. 1986). The correlation between acoustic measurements and risk of death from metastasis was demonstrated by Coleman et al. (1990).

Folberg et al. (1993) reported that the vascular pattern most closely associated with death from metastatic melanoma was the presence of closed vascular loops in primary melanoma. Coleman et al. (1995) showed the relationship between the ultrasonically estimated scatterer size and the distribution of high-risk microvascular patterns in these tumors. Based on these preliminary findings, Silverman et al. (1997) reported that acoustic spectral parameters could be used to detect and characterize these microvascular networks and thereby grade tumor lethality. These results have been confirmed recently on a large number of patients with melanoma (Silverman et al. 2003; Coleman et al. 2004). Local estimations of effective size and acoustic concentration of scattering elements displayed in the form of quantitative parametric imaging provide a method for the evaluation of microstructure changes within treated melanoma (Silverman et al. 1995).

Current developments combining 3-D ultrasonic imaging with quantitative spectrum analysis and parametric imaging have the potential to contribute to a better evaluation of melanoma (Coleman et al. 1995; Silverman et al. 1993; Yamamoto et al. 1987). Recent use of high-frequency ultrasonography has improved image resolution, decreased the volume of tissue necessary to obtain a quantitative estimate of acoustic properties and enabled 3-D imaging and ultrasonic characterization of an iris tumor at 50 MHz (Silverman et al. 1995).

To the best of our knowledge, quantitative spectrum analysis has never been used for monitoring tumor response to proton-beam irradiation. The aim of this report is to study the changes in ultrasound spectral parameters occurring during proton-beam therapy of choroidal melanomas. We also report the results on the quantification of conventional echographic parameters. The results are discussed and compared with the state-of-knowledge of *in vivo* quantitative ultrasound measurements of treated malignant eye melanomas. Some of the limitations of this study are identified.

MATERIALS AND METHODS

Patients

This *in vivo* prospective study was conducted in the Department of Ocular Oncology at the Institut Curie, Paris, France, on a cohort of 50 patients (50 eyes) diagnosed with primary choroidal melanoma. This cohort of patients was composed of 26 men and 24 women. The tumor developed either in the right eye (50%) or the left eye (50%). The age at diagnosis ranged from 26 to 82 y, with a mean age (±SD) of 61.7 ± 12.6 y. These 50 patients were treated with proton-beam irradiation at the Centre de Protonthérapie d' Orsay (CPO), France. A total dose of 60 Gy was delivered in 4 sessions over 4 consecutive days for all patients. Echographic evaluations of these patients were performed at diagnosis and repeated every 6 months after treatment over a 2-y period. Ultrasound examinations were performed by the same physician. This work was approved by the medical ethics committee of Hotel-Dieu, Paris, France. All patients gave informed consent.

Data acquisition system

Data acquisitions were performed with a sector B-SCAN COMPACT instrument (Quantel Medical, B.V. International, Clermont-Ferrand, France). The B-SCAN COMPACT provides 2-D B-mode images and the possibility of superimposing an A-mode line for measuring axial eye length and internal reflectivity of the tissues. The scanner was connected to a video printer, which allowed capturing B-scan images to document tumor size (base and height) and location for post-irradiation follow-up. The B-SCAN COMPACT was modified to have access to the radiofrequency (RF) signal. This ultrasound system was equipped with a 10-MHz center frequency, mechanically scanned transducer. The transducer had a 7.5-mm diameter and a 25-mm focal length. The −6 dB