

In Vivo Phosphorus MR Spectroscopy Demonstrates the Heterogeneous Composition of Sarcomas

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Sarcomas are a histologically diverse group of aggressive cancers. They often afflict people in the prime of life, thus, the number of years of life lost is substantial despite of their relative low incidence. Approximately 13,170 cases and 5,380 deaths attributable to these diseases are expected in 2010. With a mortality rate of 40%, patients with sarcoma are in need of accurate clinical tools for their study. Currently, sarcoma diagnosis and grading is established by an image-guided biopsy. However, needle biopsies miss diagnosis and/or grade in up to 10% of patients. This is due to the heterogeneous distribution of malignant foci in sarcoma masses, which is not made patent by the imaging techniques utilized to guide the biopsy. Grading is essential for treatment planning. Treatment options are surgery alone for low-grade and neoadjuvant therapy and surgery for higher grade tumors. When successful, neoadjuvant therapy improves the survival odds for the subsequent surgical treatment. Currently, success of neoadjuvant treatment is established by tumor shrinkage. However, evaluation of response by tumor shrinkage yields a large number of false results due to other causes of tumor volume modification besides treatment effects (i.e., necrosis, hemorrhage), and the still possible presence of malignant foci despite tumor shrinkage. Again, the inability of the standard imaging techniques to demonstrate malignant foci has a major contribution to the proper evaluation of response in sarcomas.

A noninvasive way to obtain information about the metabolism of sarcomas is to use ³¹P MRS. Since accurate localization of *in vivo* ³¹P MR spectra in three dimensions using chemical shift imaging (CSI) has been available, reliable registration of ³¹P signals to the sarcoma mass has been possible. Previous reports have shown that in general, the sarcoma spectra have abnormally strong ³¹P MRS signal intensities in the phosphomonoester (PME) and phosphodiester regions, high intracellular pH, and variable amounts of nucleoside triphosphates (NTP). In addition, correlations between several of the metabolites in ³¹P MR spectra of sarcomas and pH

with parameters of treatment outcome and survival have also been demonstrated. Our group has also shown initial results of the correlation between ³¹P MR spectral characteristics and the histological makeup of the tumor mass. We reported that a spectrum with good signal resolution correlated with predominantly cellular tumor masses, poorer quality spectra but still adequate to quantify spectral signals were from masses that contained large amounts of matrix or necrosis relative to cells, while spectra with little or no signals above the noise level were from tumor masses almost entirely constituted by fibrous or myxoid matrix, necrosis, or cysts.

In order to obtain the sarcoma spectra in previous studies including ours, either one voxel was selected and considered representative of the whole tumor mass or all the voxels inside the mass were averaged to get a single spectrum. A problem with these approaches is that due to the heterogeneity of sarcomas the spectrum selected might not represent properly the tumor mass either by missing the more important

characteristics outside the voxel or by obscuring the contribution of smaller, but potentially more important tumor regions. In addition, these approaches missed to take advantage of the spatial localization of the ³¹P signals obtained using 3D CSI.

Procedures & Patients. After approval by the IRB office, we studied the tumor mass of 20 sarcoma patients (six leiomyosarcomas, five liposarcomas, eight malignant fibrous histiocytomas, three osteogenic sarcomas, two rhabdomyosarcomas, two Ewing's tumors, a chondrosarcoma, a chordoma and an undifferentiated sarcoma) using 3D-localized, ¹H-decoupled, nuclear Overhauser enhanced, ³¹P MRS prior to start treatment. The ³¹P MR data sets were processed using 3D-i-CSI, a proprietary MRS processing program which maintains the 3D relationships of the data set.

Results. In tumors with histological information available (eight with homogeneous cellularity, three with matrix intermixed with cells, and two with extensive necrosis), we obtained an average tumor spectrum. As previously reported, average spectra correlated with histological makeup. However, when the analysis was made in a voxel by voxel basis, the intra-tumor spectra showed large differences between each other in 10 of the 20 cases studied. An example of one of these cases is shown in figure 1. The case corresponds to a 75 year-old female with a leiomyosarcoma located in the gluteal region. The histology was reported as mainly cellular with focal necrosis. After neoadjuvant radio- and chemotherapy the tumor progressed (no response) and the patient died of the disease shortly thereafter. The MR image shows a tumor mass with a diameter of 9-10 cm. The overlaid grid on the image is the projection of the 3D voxel matrix of the ³¹P data set. Six spectra are shown in their spatial location (green) and the three completely inside the tumor are highlighted (yellow boxes) and expanded to the right of the figure. The average spectrum of this case matched with the high cellularity classification (driven by the high resolution of spectrum C) but missed the focal necrosis components. Conversely, the voxel-by-voxel approach shows a spectrum that matches with necrosis (voxel A) and one with intermediate cellularity (voxel B). In addition, signal analysis showed higher PME-to-NTP ratio, lower NTP-to-Pi ratio and higher pH in voxel B in comparison to voxel C (1.46, 1.13, 7.48 vs. 1.13, 2.36, 7.07; respectively). In comparison to voxel C (and thus the average spectrum), the characteristics of voxel B matched with the ones reported for a more aggressive sarcoma prone to fail to respond to treatment as was the case for this patient. Spectra with "aggressive" characteristics but poor spectral quality were found in 5 other patients besides the one shown in figure 1.

Conclusion. Our results show that proper spectral and spatial analysis of 3D localized ³¹P MRS will help stand out the metabolic characteristics of the diverse components of heterogeneous tumors such as sarcomas improving their correlation with malignant behavior and thus outcome to treatment and survival.

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