Introduction: Liposarcoma comprises 20% of all soft tissue sarcomas (STS). Dedifferentiated liposarcoma (DDLS) is an aggressive STS subtype with 5-year disease-specific survival of 44% (1). Not only is there a need for more effective treatment for this potentially deadly tumor, but additional prognostic information would be useful in identifying patients needing more aggressive treatment. Lactate has been shown to be a marker of poor prognosis in several solid tumor types (2-5). The goal of the current study was to assess the glycolytic phenotype in two models of DDLS using lactate-edited MR spectroscopic imaging. Two different DDLS xenograft types derived from patients at our institution were studied.

Methods: Animal preparation: Seven BWH and 4 DDLS8817 tumors were grown in the flanks of SCID mice and monitored until the volume was approximately 150mm³. MRI/MRS was performed serially at 3 different tumor volumes in each mouse. Tumor volume (V) was calculated as V = (π/6)*L * W * D. MR Experiment: Mice were anesthetized with Isoflurane during the MR experiments on a Bruker 7-T Bruker Biospec Spectrometer. Two home built 2-turn solenoid coils with diameters of 10 mm and 16 mm were used. T2-weighted sagittal MR images were collected using the RARE sequence (slice thickness = 1mm, FOV = 24mm, TR = 2217 ms, TE = 40 ms, matrix size 512 X 256, number of average = 8). Lactate detection was performed using the Selective Multiple Quantum Coherence (Sel-MQC) editing sequence (6,7). Lactate spectrume was edited in Superblock-PBS (Pierce, USA) followed by hematoxylin/eosin staining.

Analysis: For whole-slice spectra, the lactate peak area was normalized by the slice volume and compared to the lactate content of a phantom section of known volume and concentration. Results: The BWH tumors grew more rapidly than the DDLS8817 (Fig-1). The BWH tumors exhibited high lactate concentrations at small tumor volumes (150-250 mm³) while the DDLS8817 had very low lactate at low tumor volumes (250-400mm³) (Figs. 2 and 3). As BWH tumors increased in size there was an associated decrease in lactate levels. In contrast, in DDLS8817 the lactate levels increased exponentially with tumor growth. Histology of large tumors showed that BWH have necrotic regions (Fig4A) and less Hoechst uptake (Fig4B) compared to the high Hoescht uptake and minimal necrosis seen in DDLS8817 tumors (Fig4D).

Discussion: Gene expression studies have shown upregulation in genes and proteins involved in cell cycle and proliferation in DDLS cells compared to normal adipocytes (8,9). In addition, genes coding for pyruvate carboxylase and phosphoenolpyruvate carboxykinase, (pck1) are upregulated in pyruvate entry into gluconeogenesis are downregulated in DDLS (10) and a recent study has shown that pck1 gene expression is independent associated with recurrence free survival in liposarcoma (HR=.72) (unpublished). Furthermore, growth rates of locally recurrent DDLS in humans have been associated with survival (11).

Based on these studies non-invasive measures of tumor growth rate and lactate production would be of considerable prognostic value for patients with DDLS. Our results show that there is heterogeneity in lactate production in xenografts derived from different human DDLS tumors and that lactate levels are higher in the rapidly growing BWH tumors at small volumes while lactate levels are lower in the slower growing DDLS8817 line at small volumes. As these are whole-slice data, the reduced lactate in the larger BWH tumors could be spatial distribution of lactate in the CSI maps with histology is ongoing. The high level of lactate in the smaller BWH tumors suggests a more glycolytic and aggressive phenotype. This work illustrates the value of MRS for noninvasively assessing tumor metabolism and providing a potential clinically translatable prognostic marker. Assessment of the relative expression levels of genes/proteins related to glycolytic metabolism such as LDH-A, pyruvate carboxylase and phosphoenolpyruvate carboxykinase is planned to determine if lactate MRS reflects genotypic differences in the two tumor lines.