Purpose: To non-rigidly register in vivo prostate medical images to regionally-graded digital histopathology (DH) images in order to determine a relationship between in vivo, fused, multi-parametric imaging and prostate cancer aggressiveness. This is a challenge due to varying prostate deformations induced by the different imaging modalities and distortion during formalin fixation and histological processing. Method and Materials: We are collecting in vivo MR, CT, and ultrasound images, as well as whole-mount DH images at 5 mm increments, from 36 RP patients. Our approach orients the physical slicing of the specimen to be parallel to the in vivo imaging planes, yielding a tractable 2D registration problem solved using a thin-plate spline method. Our technique is as follows: (1) apply a set of novel fiducial markers, visible on ex vivo MR and DH images; (2) use a magnetically tracked probe to localize the fiducials on the specimen and register the in vivo imaging plane orientation to the specimen space via a collected ex vivo MR image, specifying the insertion points of three pins on the desired specimen cutting plane; (3) use the pins to orient the specimen in a slotted forceps for slicing along the desired plane orientation. We measure slicing accuracy using a high-resolution (12.7 micron precision) mechanically-tracked probe. Results: Qualitative evaluation reveals excellent anatomic concordance between in vivo MR images and DH images, including alignment between suspicious regions on MR and confirmed cancerous regions on DH. The mean distance of the actual specimen slicing plane to the desired plane given by the inserted pins is 0.6 mm, comparing favorably with the 2.2 mm in vivo MR slice thickness. Conclusion: This work suggests our method’s potential to accurately orient physical specimen slicing to be parallel to in vivo imaging planes, yielding useful anatomic concordance between registered in vivo and DH images.