So, I'm going to try and step into the absence of Sarah and present some of the work that was done while I was at UCSF and also since then in the last couple of years since I left for maybe not greener, but different pastures. So, the title of the talk today is In-Vivo MRI and MRSI for evaluation of cancer patients. So, the phenomenon of magnetic resonance is based on the fact that, in the presence of an external ply field B, not in this diagram, there is induced in a population of nuclei that possess a quantum property known as SPIN and induced magnetization, as shown in this diagram. One of the key aspects of this that's really given rise to the breath and variety of MR techniques in medicine is the ______, which states that if this induced magnetization is somehow is displaced from the main applied field, it will process around this field and the frequency of it's procession is linearly proportional to the strength of the applied field with the constant proportionality being the gyromagnetic ratio, which is a property of the nuclei in question; it's approximately 42 megahertz per Tesla for protons. And so, take.. going from this, it was also discovered around in the mid-century that by applying second field, here labeled B1, that oscillates around the direction of the main static field at this resonance frequency, you can cause displacement of this induced magnetization away from this axis, as shown in this cartoon here. And so, this processing around this axis. And by putting an inductive coil, whose aperture is also perpendicular to the main static field, you can measure, you can convert this change in magnetic flux as this vector processes into an electric current that can be measured and used to gain some information about the distribution of spins within the patient or within any sample. So, this has given rise to magnetic resonance imaging whereby magnetic field gradience are applied to differentiate MR signals spatially based on the differences in resonance frequency incurred by the magnetic field gradience. And there are several different ways of obtaining contrast in MRI and I've shown here T2 weighted images as well as T1 weighted images and these are just.. if by tailoring the.. your acquisition sequence, you can highlight different modes of contrast based on the response of spins to changes in magnetic field. And so MR imaging has been shown clinically over the last 30 years or so to provide excellent soft tissue contrast and is used widely in cancer imaging for all sorts of applications such as directing biopsies, guiding surgery, targeting radiation therapy, selecting therapy courses and evaluating response to therapy. But, the problem is that there are a number of circumstances where conventional MR imaging doesn't tell you the whole picture where the information garnered from it may not fully distinguish between tissue types that may be of importance for cancer staging and therapy response. And so this is where, turning to other aspects of MR and other novel functional MR techniques may provide new information and allow us to improve clinical evaluation of cancer. And this is highlighted in this slide, in which I've shown a panel of gliomas of three different grades and four different cases for each. And what you can see is that there are a variety of presentation types for this tumor type in particular. This is evidence by, as in grade three, where some of the tumors contrast enhance.. that is they, upon injection of a magnetic.. or an agent that affects the relaxation of spins, some of these tumors have broken down the blood brain barrier and allow this agent to extravasate and accumulate in the extracellular space, thereby giving you an increased signal, but some of them don't. Further more, the basic problem is that it's very hard or.. to assign a specific tissue type to these images based simply on grey levels or by using some kind of morphometric information. So, and also this is just telling you basically about the structure of tumors. As Dr. Ling said, there are.. is increasing justification for wanting information about the physiologic metabolic behavior of these tumors as it might provide further information on how to stage them and prescribe effective therapies. So now I'm going to turn to discuss some.. a couple of emerging techniques. I'm going to focus

mainly on magnetic resonance spectroscopy, which is really antecedent to imaging in that this was.. has been used by chemists for years to lucidate chemical structure and is now, in the last fifteen years or so, being applied In-Vivo clinically… routinely clinically now to look at different metabolites and their distribution In-Vivo and use that information to deduce what types of metabolism are going on in tissues. I'm also going to touch on dynamic contrast imaging, which can be used to look at vasculature within tissue and finally with a diffusion weighted imaging, which is a specialized type of MRI, in which gradience are applied so that the signal produced in the images is related to the diffusion of water.. protons in water within the subject. Their even.. this has been developed to the point now where using appropriate sequence, you can actually fully measure the

diffusional tensor. So the fundamental idea of spectroscopy is it goes back to the ____ modified version. I mentioned that the procession frequency is linearly related to the magnetic field experienced by the spins. Well, the issue, the crux of spectroscopy is that this field is affected by the chemical surroundings of the spin in question. So, for example, a spin in water will have.. will experience the field as mediated by it's.. the other spin and the oxygen atom in water whereas the effects of say on the magnetic field experienced say by a spin in ethenol will be significantly different and that will affect this spin and thereby affect the processional frequency, which is something we can measure. So if you look at a MR spectrum so this.. the horizontal axis is frequency here, this is an MR signal obtained from brain at 1.5 Tesla and basically what you see is scaled so that

maximum signal is a single peak, which is water and this is just because water is present in so much.. in such a greater concentration than anything else in the.. any other proton spin in the body. And this is what gives rise to MR. MR focuses on this water signal because it obviously, as you can tell from this spectrum offers the best signal to noise and gives us the most signal to work with in order to generate an image. However, if we blow up a separate section of this to a greater resolution, what we can see is that there are other signals in this brain spectrum that can be measured and have been assigned to other metabolites. In this case, there are several that are choline, creatine and NAA, which I'll talk about in a second and what is being done currently at UCSF also at other places, Sloan Kettering and Mass General is correlating these signals with biopsies samples that

are taken out and sent to high field spectrometers, where you can get much greater information; a much wider range of metabolites and greater resolution between the peaks. So spectroscopy really has a lot of capability for identifying for In-Vivo between, say three to seven and Ex-Vivo up to, say twenty to thirty independent metabolites that can be used to identify the specific metabolism within tissue. So for In-Vivo, which I'll focus on, there are, as I said, it is easier for brain spectroscopy, there are about.. a given, say, assuming 1.5 Tesla scan and standard commercially available press excitation sequence, there are about five metabolites that can be independently identified. The first is choline, which is a neurotransmitter in a membrane component and has been seen to increase in tumor presumably because of increases in cell division and the need for increased

membrane manufacture and metabolism. Creatine is a cellular bio-energy reservoir. NAA is the other one I want to focus on, which is a neuroma marker in the CNS and it's not present in other cells in the nervous system, so it can be used as an identifier of the presence of neurons in the sample that you're looking at and in tumor cases, it decreases because of the depth of these neurons as they're encroached upon by the glial derived tumor cells. And finally, there's also lactate, which I'll touch further on in a second and lipid which are.. actually occupy the same frequency band in the spectrum and I'll discuss a new technique for separating these two later on in the talk. So, originally what was done in In-Vivo spectroscopy was a single voxel.. they basically picked out a single box.. let me go back here.. to pick out a single box in your subject and acquire a spectrum from

that, but more recently, what has been done is combine the pulse sequence for imaging involving gradience, so these are the gradience in X,Y, and Z and combining that with the spectroscopic acquisition so that you can now acquire an image.. a 3-D image, in which each pixel contains not a single intensity, but an actual MR spectrum so you're obtaining an array of spectra that can be analyzed both for their individual metabolic content as well as there spacial distribution. So, this is an example of an MR, a slide data set. This is a single slice extracted from a grade 4 glioma and this..so this is super imposed on the MR image here, showing that.. so this is a contrast enhancing glioma here. It's got a central necrotic core and it's as.. if you look at the spectroscopy information, what you can see is that.. you see these tumor suggestive patterns, in which the choline is elevated,

the NAA is decreased, infiltrating out into the surrounding tissue. You've also got normal patterns, which are removed from the tumor, but the interesting thing is that the distribution of these patterns is significantly different than the distribution of contrast enhancement in the tumor, suggesting that this could provide an alternate method of identifying these tumors and potentially targeting them for therapy. In terms of the necrosis in the tumor, what you can see is that in these areas there is a.. all the metabolites have decreased and there is also an accumulation of lactaid and lipid here, which is indicative of cellular breakdown and the breakdown of the cells that have died here in the center of the tumor. So, one of the problems with this is just how do you go about analyzing this clinically. This is a fairly complex data set. It's one thing to show

an image to a radiologist and ask them to differentiate things anatomically. It's quite another to give them something that looks like this and ask them to interpret this and what this implies for the management of this tumor and so what Tracy McKnight at UCSF has spent the last three or four years developing and validating methods of analyzing these data sets statistically and generating maps of so called abnormality or the statistical likelihood that a tumor is suggestive.. or that a voxel.. spectrum from a voxel is suggestive of tumor and what she's done basically is model the relationship between NAA and choline in a voxel as a linear function that's dependent on the tissue content of the voxel. So, the assumption is that normal tissue has basically a fixed NAA to choline ratio. This isn't exactly true, but it works for the purposes of this analysis. And then

what you can do is analyze the deviation of choline and NAA for normal and assign overall deviation from this.. the so called normal NAA to choline on a per patient basis. What this results in, is for each voxel in the data set, you come up with a number from 0, meaning it's perfectly normal, up to whatever.. up to whatever level increasing numbers, meaning that this voxel is more and more different from the normal population. And so this is shown for this data set here, where you can see if you look at the spectra here, these are clearly abnormal with an elevated choline and reduced NAA and this is reflective in this index. And then for the purposes of analyzing the impact of MRSI, what has been done is this low resolution data set.. these are typically acquired one centimeter resolution, is then re-sampled to approximately the resolution of the MR data set and

contoured at different values. The green is abnormality index of two, the yellow is three and the red is four. And these can be analyzed relative to the MRI appearance and used to assess the impact of the MRSI data set on a clinical evaluation of these tumors. So, in terms of gliomas, these just.. some statistics on what this.. what these numbers actually mean. And so first, what was done was the difference non-tumored tissue and tumor tissue is assessed in terms of these endosis and what was done several thresholds were chosen looking to differentiate these two and sensitivity specificity were analyzed. You can see that here.. very sensitive for differentiating these two in the specificity improved slightly as this has increased with the optimal cut off being approximately 2.5. So, what that means is that a cut off of 2.5 can be used.. a contour of 2.5 can be used to identify the

region of the data set, which MRSI indicates is a likely tumor. And also the distribution of the CNI values over different grades of tumor have been evaluated. You can see that for, actually the trend is that for increases from grade two to grade three, the maximum CNI. And then actually decreases for grade four so it's not a linear trend with grade and this is thought to reflect the fact that these grade four lesions contain micro-necrosis that tends to "dilute the spectral signal" cause.. so that you have, instead of having simply tumor, you have an average of tumor and necrosis and this results in the choline levels being less than those of grade three, which do not have necrosis. And so Andrea Pursecol has done analysis relating these.. these contours.. these MRSI derived contours to the MRI occurrence of a lesion and shown that there is significant difference between them,

both in terms of deviation between the maximum deviation in terms of linear distance between the two as well as simply in volumes with.. so the volumes that the CNI and the T2 abnormal region are approximately equal, but there is still significant differences between the actual contours whereas the.. all four.. all three of these analyzed contours are much bigger than the contrast enhancing region suggesting that this region doesn't very effectively identify the presence of tumor. I'm just going to touch a little bit on some work that I did and has been continued in terms of use of MRSI in radiation therapy. This study was basically done to show, well so these are patients that were treated with GammaKnife and what we wanted to show was that if you have a prescribed radiation target here and you have abnormal voxels beyond that target, does that say..

imply anything for the prognosis of the patient. So we've stratified these two cases and looked at survival and these are basically two different.. the green is Case A, where all the voxels were.. that were considered abnormal were actually treated with up to a certain percentage of radiation and this.. the red is this other case where there were voxels outside this target. And what you see is there is a difference between these two that was statistically significant and this is just survival. And these two plots just show two different way that we've used of identifying the presence of these abnormal spectral voxels and they both give statistically significant results suggesting MRSI has something to say about which patients are going to respond better to therapy. So what does this imply? Well, if the patients who have a spectra that are outside the target do worse, well

maybe it's.. it would be useful to then target radiation therapy treatments to the region of spectral abnormality. Now, this is a bit of a problem because of the poor resolution of the MRSI data set. And so what the operational protocol is right now is to basically take this, re-sample it to a higher resolution, contour it and then target treatments to a certain contour.. there it's actually.. it's not a straightforward algorithm right now. There is basically all the regions that have a CNI of three or greater are targeted and then the radiation target is adjusted to the CNI II contour based on physician discretion. This gives a means of basically targeting these abnormal voxels and allows us to see perspectively whether this will have an affect on patient response. So, this was the case of actually looking at that response with spectroscopy and looking at radiation response

in terms of its spectral appearance. So, this is a patient who was treated with GammaKnife for this contrast enhancing lesion and this was the evolution of the tumor two months and three months post therapy, so there's obviously an increase in contrast enhancement post therapy. Now, one of the problems and one of the motivations for using MRSI is that this increase in contrast enhancement and the breakdown of the blood brain barrier could be due to either tumor progression or it could also be just a radiation effect that is independent of the growth of the tumor and so we could look at this via spectroscopy and what's interesting here is that again we see the presence of abnormal voxels outside the what was treated so, in addition to being tumor inside the target, there's also tumor widespread outside the target. And after treatment, what we see is that

there is a moderate response within the target and there's development of lactaid and lipid in here suggesting the radiation has killed some of the cells, but this tumor outside persists so this is most likely actually tumor that was present at this time point, but not identified based on the MRI and it's now progressing and becoming clinically problematic and this was verified by histology after the patient went to surgery. We can also look at XRT and I'm going to kind of speed this up because I'm dawdling on the MRSI a little bit. But we've also looked at response to XRT using these same techniques and I looked at.. the interesting thing about XRT is that given the dose fractionation schemes, you see a number of different patterns in the spectral.. as in the spectra as they evolved. And so here, in a voxel that was in the center of target, you see a decrease in all

metabolites and the trend for necrosis suggesting response there and then similarly in voxels outside, we see an evolution towards a tumor suggestive response. The interesting thing here is in voxels that were in a lower dose region, along these white matter tracts around the ventricles, what is observed is a gradual decrease in all metabolites. There is still a normal pattern preserved here, but all the metabolites go down at the.. by the two month time point and then slowly recover suggesting there's some kind of sublethal damage or subsequent damage repair that's going on in this tissue. So this is, I think, a very interesting application of MRSI and this is actually about to be published and it's been further continued by post-doc in the lab, Michael Ling, who's been using MRSI to look at normal tissue radiation response in these kind of patients.

So, I mentioned lactaid and Dr. Ling also mentioned the utility of lactaid and it's interest in measuring hypoxia, so the problem with lactaid is that it occupies the same frequency band as the lipids, so if you measure a peak here, typically its difficult to identify what.. whether that corresponds to lactaid or lipid or some combination or both. So, what's been done is lactaid edited MRSI sequences have been developed and by lactaid edited, I mean the pulse sequence is designed such that there are actually two acquisitions that are received and by using linear combinations of those and by affecting the phase of the lactaid protons preferentially relative to the lipid protons, you can independently resolve these two. And this is now being used clinically. It's slightly longer examination, but can be used to identify lactaid and look at its prognostic significance in gliomas. And

additionally John Kerhanowitz and his group at UCSF applies all these tests.. same techniques to prostate cancer and acquired similar favorable results in terms of being able to identify tumors. In this case, choline is also a negative marker indicative of the presence of tumor at the normal marker in prostate is citrate, as shown here, which is produced by, I believe, the ductal cells in the prostate, normal ductal cells. And so as tumor progresses, this citrate.. the levels of citrate are decreased by.. because of the absence of these cells undergoing normal metabolism. And so you can treat this similar to NAA in that you're looking for simultaneous elevation of choline reduction of citrate. And this has also been used to look at Brakey therapy in prostate cancer patients. You can see here, really at a pretty dramatic difference in terms of cells that were initially.. so

there's presence of tumor indicated by the MRSI data set. Before administration of Brakey therapy and after Brakey therapy, basically all metabolism in the prostate had been destroyed and killed all these cells. So, now I'm going to just briefly touch on dynamic contrast imaging, which is in keeping with the theme of the session. A second modality imaging that can be applied using, interestingly, the same acquisition hardware, so where in PET, you need different radiotracers to look at different metabolism. All these are basically variations on pulse sequences and also here are contrast agents are used, but the hardware needed is all.. in all cases the same conventional MR hardware. So, what's done here is the contrast agent is injected and images are acquired very rapidly over the first pass or over the first couple of passes of this agent through the tissue and by mottling this decrease in signal.. this time dependent decrease in signal as the agent passes through the vasculature, you can deduce some information about blood volume and I will touch.. I have some follow-up slides to this that I will get into and also I mentioned diffusion weighted imaging, in which you can map out the diffusion tensor and the idea here is that in, particularly in the brain, there is very ordered growth, very structured.. very well structured morphology of tissue in the brain that leads to the diffusion tensor being very isotropic in order. And in the presence of tumor, this structure is lost and so you can identify tumors by a relative change in the appearance of the diffusion properties of water in the tissue. And so this is shown in the relative anisotropy map where, in tumors, the anisotropy is increased because of the loss of the

structure. So, to put this all together and try and wrap this up so.. I think I'm running over time here, basically what's being done now is combined studies. As I mentioned, this can all be done on a single hardware platform. And so you can acquire all these data sets for patients within the same hour to hour and half examination and this is being done across different grades of tumor. And I just want to touch on this interesting stratification now since it was done recently by ____ ____ Lee at UCSF, in which he took basically these individual pieces of information.. these multi modal pieces of information including central necrosis, leaky vasculatures as based on the appearance of MR and then cellularity and the hypoxia, which this is just an idea that classification scheme, but use these to stratify patients and show that she could distinguish different grades of tumor

based on these kinds of parameters deduced by the MR information. And furthermore, what she did was then looked at prognosis based on these and came up with the stratification system that includes first of all age is still, for brain tumors, one of the most important prognostic factors, but then using things like the presence of lactaid and lipid, the choline level relative to the creatine, the volume of contrast enhancement and the creatine level relative to the NAA and showed that she can really stratify.. get very striking differences in survival using this kind of stratification scheme. So, this is being analyzed now as a means for identifying.. providing prognostic information for patients and using that to select therapies for them and optimize their clinical management. So, I'll sum up now that I'm about.. oh three minutes over. So multi-modal MR techniques

are really clinically feasible at this point and their very complimentary of MRI and allow the acquisition of a range of different types of information from diffusional characteristics to metabolism to vascular performance in the clinic for both brain and prostate cancers as I've shown here. And so, these studies are ongoing. Further validation is needed to document some of the, kind of initial suggestions of these studies. And I didn't have a chance to mention, but also, a lot of this.. all this work.. 90% of the work that I showed here was acquired on a 1.5 Tesla scanner and now with 3 Tesla scanners emerging and becoming more common place in the clinic, in theory, for MRSI, this should basically double your signal to noise and allow you to move to smaller voxels that may be more useful for further applications such as treatment, planning and also give

you better resolution of individual metabolites and maybe allow you to see a couple more and assess their impact on evaluating cancer. So, in conclusion, I'd just like to thank both the research staff at UCSF that helped me while I was there and as well as all the clinicians that are involved in these projects in both neurosurgery, urology and radiation oncology. Thank you for you attention.