Good morning everybody. I am going to talk this morning about use of CT and PET and radiation therapy and, first of all, I would like to thank organizers for giving me an opportunity to give this presentation. This is the third year in a row that I'm giving this, so, hopefully, most of you haven't seen it and it will be new material. Basically, what I would like to cover today is, what is multi-modality imaging have to offer in radiation therapy? How is it going to change what we do? We have used different imaging modalities for a while, but really, I don't think we have fully exploited the potential and I show some examples of what we have to gain from different imaging modalities and how it can have a strong potential to change our practices. We'll talk a little bit about the current status of a CT technology that's used in radiation therapy. We'll talk a little bit about a PET technology, influence of PET in radiation therapy, and I'll

show a couple of examples of how PET can be used for treatment planning, and then we'll have some conclusions at the end. As we know, most of what we do is image guided. The 3-D radiation therapy really would not exist without **volume-matrix** images. CT has been the primary imaging modality and will continue to be the primary imaging modality in radiation therapy; however, I think there are other imaging modalities, there are slowly, and some faster, making their way into our clinics and also, more importantly, I think they're used outside a clinic to guide what we do in radiation therapy. MR and functional MR is probably limited to cranium right now, but I think that there is a fairly fast push to go to extracranial MR. Nuclear medicine imaging, SPECT and PET, I think, has made a giant leap over last few years, and ultrasound has been with us for a long time. And, finally, molecular imaging, which I will not talk that much

about today, is…there's a lot of research in basic sciences in animal imaging, and, I think in years to come, molecular imaging and the imaging of functional processes will come to radiation therapy. I think if we had a sentence that can sort of summarized what we want out of imaging as a whole in radiation therapy, would be to accurately delineate and biologically characterize an individual tumor. Well, what does that mean? Basically what happens now if a patient comes into radiation oncology department, we treat him based on a stage; we do not differentiate between individual tumor types. Tumors…patients are typically treated as a statistic rather than looking at individual tumor properties. So, often what happens, we have two patients, that have a same stage, we…that have probably similar socioeconomic background, and we treat them the same and one patient does very well, the other patient does not do as good, and probably one of

the reasons why there's a difference in the outcome is because we do not appreciate the individual, biological properties of these tumors. So, what we're looking forward from imaging modality is to be able to tell us what type a patient's tumor is and how we need to treat a tumor, and that would be, basically, the next part of a sentence--we would like to be able to select the appropriate course of therapy using the imaging data so we don't treat again a patient inappropriately, but we would like to know more about the **definitive** individual tumor property. And, finally, we would like to be able to predict the response at the earliest possible time. Ideally, we would like to know how to treat a patient at the time of staging, or the time of disease detection, and be able to predict the outcome fairly accurately, and we'll talk about that in a little bit. So, really, the imaging information can be divided into anatomical and biological.

Anatomical is really what we've been doing thus far and biological, I think, will make its way reasonably quickly with the next, probably, five years, and we will know more about metabolic, functional, and physiological properties of individual tumors and we will be able to stratify patients no only based on stage, but also based on individual tumor properties. So, when we talk about the potential multi-modality imaging in radiotherapy, some of these things have already been implemented, but one is, certainly, I think we can detect tumors earlier and probably define them better. What happens now, we actually wait on patient to have either clinical symptoms or to have an anatomical manifestation of disease. Well, anatomical manifestation of disease is typically late…late changes in anatomy of some processes that happen a long time ago on a molecular level, so if we can actually image on a molecular level and if we can change…if we can image…image changes in physiological processes, we should be able to detect tumor earlier and catch patients at earlier stage. Now, what that can do, these patients then may be surgical candidates rather than radiation therapy candidates, and that will probably change how we…the group of patients that we treat; but, nonetheless, it could improve the overall patient management. Staging is another important part and I will show from the next slide that functional imaging can improve staging and with more appropriate staging, we can treat patients better. What does that mean? Well, basically, if the patient is palliative patient where disease is probably more extensive than what we can get from only anatomical image; from CT, we may be able to avoid unnecessary curative treatments in the patients that really cannot achieve the long-term disease control, so that can improve the patient's quality of their life and also quality of the management, and it can also have a financial income on medical care as a whole because we will not give unnecessary treatments. And, this is one of the examples from what we've been doing at our institution for a while now, we've been staging cervical cancer patients with PET and, if you compare the CT ability to detect positive lymph nodes in a pelvic region, para-aortic region, and a superclav to those to PET, you can see that PET does a much better job of finding the true extent of the disease. So, for example, what would happen with these 7% of the patients out of 256 that have a negative cervical lymph nodes by CT alone, these patients would be treated curatively, where, in reality, their disease is spread too far and they will not have a positive outcome, so PET information in this case would certainly give us more appropriate course of therapy for these patients. And, basically, if we look at the survival curves, they do support what…what we just looked at. The…this graph here is for the pelvic lymph nodes and this graph here is for para-aortic lymph nodes, so the patients that had a negative pelvic lymph nodes by CT and PET, they do, by far, the best; the bottom curve is the survival curve for patients who had positive pelvic lymph nodes by CT and PET; and then the middle curve is really the interesting one, these are the patients that had negative lymph nodes by CT, but positive lymph nodes by PET, and this is the group of patients that we will treat differently if we did not have that information, and that difference is even more striking when you go to the patients and look at para-aortic lymph node a moment**,** these are patients who had negative para-aortic lymph nodes by CT and PET, the patients that have positive para-aortic lymph nodes by CT and PET do fairly poorly, and so do the patients that have positive para-aortic lymph nodes by PET; but these patients, interestingly, would…they have a negative CT nodes…they have negative para-aortic lymph nodes by CT. So, what would happen if we had CT alone, this group of patients, and this group of patients, would be treated the same and from their overall survival curve, you can see that that's probably not a reasonable expectation and by having the functional data, we can actually stratify these patients in two separate groups. Furthermore, what we can improve with functional imaging, or the multi-modality imaging as a whole, is a target definition. We can, hopefully, appreciate the true extent of the disease or better appreciate where the disease is and where microscopic extensions are and have a better anatomical volumes. Also, what we can do is have areas of importance within the things that we can see. We know that not all areas of anatomical deformations have same properties and Dr. **Cliff Ling** from Memorial proposed a concept of biological tumor volumes, or BTV's**,** where certain portions of a tumor are given

higher importance based on their biological properties, and, basically, what we have here, this is a patient who has head and neck cancer and the yellow line is the tumor outlined on the CT scan, and here is the Cu-ATSM…PET scan of the same patient in the same area and, basically, the Cu-ATSM has been shown to indicate areas of hypoxia, and we know that hypoxic volumes are more radio-resistant, so in this case we would use the PET information to identify hypoxic regions of the tumors outlined on the CT and then presumably we should treat these tumors more aggressively in order to achieve control. And, this is one of the figures from Dr. **Ling's** paper from 2000 where we still have the concept of the GTV, we have the concept of the PTV, but in addition, we have now areas that can be identified by different imaging modalities as having increased importance and, presumably, we would like to give higher doses to these regions. So,

this is where IMRT can come into play and allow us to modulate the dose within the targets, so rather than delivering uniform dose to the entire target volume, we can differentiate areas of increased importance, and this is sort of the concept of dose-painting. We will paint higher dose within the target volume and try to deliver non-uniform doses. Now the question becomes, how much dose should we give? In the past, all of our clinical experience is based on delivering uniform doses to the target volumes. If we want to have this biological concept, one of the questions that we don't know is how much dose do we need really to control, presumably, radio-resistant volumes. So, one of the studies that we did is to see whether we can give, for example, 80 Gy to the areas that are shown to be hypoxic on the Cu-ATSM scan and then the other…the rest of the volume is treated to conventional dose levels while we can still give less than 30 Gy to

para-aortic lymph nodes. So, this is clinically feasible and probably what's needed at clinical trials to see or to demonstrate whether this makes a difference in the overall disease control. The Cu-ATSM works in other sites as well. One of the things that we're looking now is trying to stratify cervical cancer tumors based on hypoxic properties, so this is a cervical cancer tumor that has a uniform uptake, and this is hypoxic cervical cancer, so, for example, if these two patients walked into radiation oncology, they should not be treated the same. We know that they will not have the same outcome, or most likely they will not have the same outcome based on the biological properties of their tumors, and this would be one of the examples where functional imaging can be used to stratify patients based on tumor biology. Next thing that we would do from imaging information-based therapy would be to decide how the patient should be treated

best. Based on individual patient properties, hopefully we can stratify into either chemotherapy, radiation therapy, or combination-variation therapy. And one of the goals or hopes that we can have is to incorporate imaging information into biological response models and actually have optimization programs which can tell us what would be, presumably, the best or the ideal way to treat the patients and what should be the combination of chemotherapy, radiation therapy, or combination of the both; and, I think, also what will happen because we can see things that we haven't seen in the past, we will certainly develop different treatment techniques or we will modify existing treatment techniques to adapt to imaging information, and I will have a couple of examples again where we used functional information to modify what we have been doing in the past. And, finally, one of the things that we would do…like to see from imaging is to evaluate the response to a course of therapy. What happens now, we treat the patient and then we either wait for the manifestation of the disease to disappear clinically or we image the patient two or three months later to see if there are any anatomical changes. Unfortunately, if you wait two or three months later, if it's an aggressive disease, and in many cases if it's not, it is really too late to modify the course of therapy and it's also possibly too late to initiate the course of salvage therapy. So, what we would like to do, image the patient as soon as possible after initiation of therapy and see whether what we are doing is appropriate, whether we see a response and, if not, altar the course of therapy. Now, what we would like to do is actually image at the molecular level because these changes happen in the molecular level rather than wait for these anatomical manifestations. So, the question becomes, how soon after initiation of the therapy can we image the patient. One of the things that we're doing now for cervical cancer patients, we do six fractions of HDR, we image the patients after 1st, 3rd, and 5th fraction, and we try to correlate the tumor volume to the outcome as a function of time. And, also, one of the things that we may be able to evaluate prior or even after initiation of the therapy, is the normal tissue function and use the functional information contained in these imaging modalities to decide which portions of normal organs are more important than the others and base treatment plans on that function rather than treating all of the organ as having the same importance. And this is one of the examples of the use of PET in a follow-up. This is the pretreatment scan, this is a post-treatment scan, and we can see that there's a difference in the uptake in the cervical region. If you actually look at the overall survival of cervical cancer patients—again, this is some of the work that we've been doing—if the patients have no uptake after the course of radiation therapy, the top survival curve is for that group of patients; if there's a persistent uptake, those patients don't do quite as well; and then if there's any new uptake in the cervical region following a course of radiation therapy, those patients do not do well at all. Now, when it comes to imaging for radiation therapy, we're a little bit different diagnos…than diagnostic…than our diagnostic colleagues, and one of the things that has happened in the last three or four years, typically what in the past, the manufacturers would do the…they would design scanners or they would design technology with diagnostic purposes in mind. In the last few years what we've seen were the scanners or the imaging equipment actually has features that are designed specifically for radiation therapy and I think we are recognized now as an important part of their market and we are seen tool that allow us to image patients in a…for one in a treatment position that will be used for treatment. I think that's fairly important. That's one of the main differentiations between imaging for radiation therapy and imaging for diagnostic purposes. For diagnostic purposes, scan geometry is generally less important. For us, in most of the cases, we would like to image the patient in as close a position as we would use for the treatment and having scanners which will accommodate that becomes fairly important, and I will talk about that more importantly when it comes to PET imaging. When it comes to what we can purchase today for imaging radiation oncology, you know, the basic option would be a 70 cm gantry opening CT scanner, which is a single-slice scanner acquires one image at a time; then we have a 70 cm multi-slice scanner and there's 16+ scanners available on market. I think there's a 40-slice and 64. Then we have a large-bore scanner, which, basically, the scanner opening is 85 cm and it's a single-slice scanner, and

then we now have multi-slice CT scanners with the large-bore openings, and the scan field of view varies amongst these scanners and scan field of view is fairly important for us. It may not be as important for diagnostic people, because, typically, they can cone down on what they need to image and then would need to appreciate the full external anthropology of the patient, plus to be able to calculate treatment plans and IMRT, we need to know the full extent of the patient and the scan field of view of how large object we can image with the CT scanner is fairly important and this is also one of the things that the manufacturers have changed on their scanners. Typically, they used to display up to 48 cm, now the scan field of view has gone up to 60 cm and I think largely that was driven by radiation oncology. Next, we have PET/CT combined units in a number of radiation oncology departments have these. There are MR scanners that are making

way into radiation oncology and one manufacturer has, actually, an MR simulator that's designed very similarly to a CT simulator and it's meant to have a same process. One of the limitations in the past, and what we used to do for CT imaging, was the x-ray tube. Again, the x-ray tube was designed with diagnostic radiology in mind. Typically, in diagnostic radiology what happens, they get fewer number of slices, they get thick slices, and they do not have to get slices as rapidly…images as rapidly as we do. Often, what we would like to do is get quick scans where the patient does not move from upper thorax to a lower thorax, we would like to get thinner slices to improve the image quality, and also we'd like to get large volumes. Well, every time that you create an image with a CT scanner, you store certain portion…certain amount of heat on the x-ray tube. Eventually, the tube exceeds its heat storage capacity and the scanner

would have to stop; so what we've done in the past is either we scan thicker slices, we scan shorter volumes, we reduce mA, which reduces image quality, we increase pic…typically, we would either sacrifice the amount of information that we image or the image quality, and that technique has changed with introduction of multislice CT scanners. In 1992, Elscint, a company from Israel, introduced a first dual CT scanner where, basically, on the other side of the patient, away from the x-ray tube, there are multiple detectors creating multiple images for each rotation of the tube, and in 1998 four-slice CT scanners were introduced, and, again, there are multiple-slicers available now. Well what does a multislice scanner do in radiation oncology? For one, it's essentially faster. Most of the multislice CT scanners are capable of half-a-second rotation. So, for example, if you have a 16-slice scanner capable of half-a-second rotation, in one second you

can get 32 images. At the same time, for the same duration, for one second on a conventional scanner you only get one image. More importantly, for roughly the same amount of heat, you get many more images in a multislice scanner than in a conventional scanner, so the tube heat storage capacity becomes less of an issue. So, in a sense, you now have an excess of a tube heat and you have a choice of what to do with that tube heat. You can either get thinner slices, get more images, you can get…you can put, certainly, more mA…mAs in these images, presumably, get the better image quality. Also, these…these scanners would allow us to use thinner slices, which would, hopefully, improve the spatial resolution. So, the things that we will want to see or the things that we're expecting from a multislice scanner would be faster scanning, hopefully, better spatial resolution, and also better image quality or low contrast resolution. Another thing that we can get is more images, thinner images, and on this side, this is a DRR created with 3 mm slices, this is a DRR created with 1.2 mm slices, and, clearly, this is a much better image and

containing much better resolution in the detail and, hopefully, can be used to better position the patients on a daily basis, or to verify their position on a daily basis. Now, one of the problems that we have is that, I think, the imaging technology has probably surpassed the capability of treatment planning technology. This scan, for example, is 30 cm long, there are about 100 images. On the other side, if this is the same length image, there about 250 images, or 2½ times more images. Well, 2½ times more images means that there are 2½ times more images to contour, there are 2½ times more images to store, and there's twice and a half…or 2½ more times data to process while we do treatment planning, and this number of images would slow us fairly substantially and cause some problems in the treatment delivery process. So what we're looking for from manufactures is a capability to process large number of images, have studies

that 400 or 500 images, but in an efficient manner similar to what we've been doing now, and I think they're trying to address these issues in some of the schemes, for example, where maybe we see only every third image in the treatment planning computer, but in the background the entire **volume-matrix stats** maybe of 500 images exist that will be used for DRR calculation, and I think they're fairly…they're working on tools that will allow us to process larger number of data, but at the end, with the…with the…with the multislice CT scan we can get very high quality images in fairly short time with much higher mAs than in the past. Another benefit, and, yes, there have been a number of talks on this is, 4D-CT, basically, trying to image patient motion with a CT scanner. One of the things that we do at our institution, we acquire multiple sections of patient at a time, basically, let the patient be scanned in a sitting mode where the

couch does not move while the tube rotates so we will get one section of the patient, for example, for 16 times, or 12 times, then we would move the couch and let another 16 images acquire the same location and then patient's connected to a free breathing spirometer and using the **total** volume, we would reconstruct these images and, basically, get the pictures of how the tumor moves as a function of time, and then we can use this information in the treatment planning process to determine either what the tumor…what the treatment vol…or the PTV margins should be, or to modify the delivery techniques. So, I think this will definitely be a fairly important part, and I won't go into greater detail since there were a number of talks yesterday. Another important part of CT technology is the bore size and I think it's been now shown fairly well for what we do, we really need larger bore scanners than 70 cm, and, for example, this is an 85 cm

scanner and this is the same scanner with an insert that brings it down to 70 cm and treating a patient in a **sedentary** position is fairly difficult; this is a bilateral patient; and this is a patient that has **(--?--)** coma and, again, this patient could not be scanned in a treatment position on a conventional scanner. So, one of the things that has happened, and this is why I'm saying that radiation oncology has driven a little bit of what manufacturers are making, is now we have large-bore scanners that have a multislice capability and all of the three major manufacturers have one. This is Siemens SOMATOM Sensation; it's an 82 cm bore opening, 16-slice scanner; GE has an 80 cm opening with a 4-slice scanner; and then Philips is coming up with the 85 cm scanner that's also multislice CT. So, I think in the near future the question will really become, how large? I think the 70 cm question will sort of go away and mostly what we will be buying

for radiation oncology purposes will be 80-85 cm and then there's the question of a single versus multislice, I think single slice has large use for a number of sites, but then when it comes to thorax, I think the multislice would offer advantages that single slice cannot, and the question really becomes, how many slices do you want? Not only do you want one slice, but do you want 10, 16, 40, and so on? And, finally, there's a thing that may happen in the near future with the…with the sort of rapid growth of combine CT is maybe the possibility of coming back of a Sim-CT where a conventional simulator capable of tomographic acquisition and **(--?--)** have a product a few years ago that would get one slice at a time and that was fairly slow, but now with the combine CT, they may be able cap…they may be capable to get **volume-matrix** CT images from **broad rotation** over conventional scanner and that may change a little bit what we do.

Another thing that's happened for a number of manufacturers is we're trying to eliminate the step of having to transfer images from the scanner to virtual simulation software and then wait…have the patient wait on the couch and feed that information back. What we would like to do is for a CT-simulator to become really one unit. You have a CT scanner and on the CT scanner control console you have tools that allow you to contour and to localize the tumor during the simulation, so rather than having a diagnostic scanner, which was designed with software for diagnostic purposes, now manufacturers have scanners that have radiation oncology tools which will, hopefully, help us better or more efficiently simulate patients. So the idea is to eliminate the virtual simulation part, get the patient, get some contours on the scanner, and then, from the scanner, straight go to the treatment planning system, and basically this is…this is an image of

one of our CT scanners that does have a capability of contouring and localizing tumors on the scanner and, basically, virtual simulation tools is on the control console where technologists or therapists initiates the scan, the physician starts contouring as the images are coming in, we localize the center of mass, and we mark the patient accordingly without having to send the image somewhere else. So what happens, physician contours the target and then the software tells us where to place the lasers and the table to mark the patient. So this…this has actually fairly, significantly speeded up the process of marking the patient, where in the past it would take four or five minutes to transfer images to another work station, to pull them up, to import them; now we do this in about a minute and a half to two minutes. As images are coming, we contour, and as soon as, you know, most of the images are in, we mark the patient. When it comes to PET

for imaging radiation therapy, and now we'll shift our concentration for a moment, one important thing about PET is it provides a physiological information rather than anatomy. The actual anatomical definition of PET images is very poor and if you want to use PET in radiation therapy, almost always you will have to mate it to a CT image or you will have to register it to a CT image. So, with diagnostic purposes, you know, how the registration happens is really not that important. They can actually look at the scans side by side without actual registration, but with treatment planning purposes it is very nice and very desirable to have these images registered to each other. One of the problems is the extremely poor resolution. On PET images, most of the time you have a hard time appreciating the skin much less the internal organs and the software tools, or the hardware tools that allow us to register images more accurately and more efficiently go a long way. One of the main imaging agents in PET is FTG, or fluorodeoxyglucose, and it's a sugar analog, it works very well in a large number of sites;

however, FTG is fairly limited when it comes to slow-growing tumors or, for example, for identifying hypoxic regions. So there's a whole slough of imaging agents being developed or being used to image processes other than just the metabolic processes in the tumor; so, for example, this is a patient who underwent a radical prostatomy and who has still persistent PSA, and this is a FTG PET scan of the same patient, the patient has positive pelvic lymph nodes, but it's kind of hard to appreciate them on FTG scan, but if you look at the carbon-11 acetate PET scan, it's fairly obvious where these lymph nodes not…lymph nodes are. On a regular nuclear medicine scan, it's almost impossible to see them; and on a CT you do actually see them fairly well as in large nodes, but this is what we're hoping for. We're hoping for that other imaging agents are being developed that will give us information beyond only metabolic information of

the slow-growing tumors. Now, when it comes to imaging for radiation therapy purposes, with PET there are two options: you can have a separate CT scanner and a PET scanner and register that information prior to importing into a treatment planning system, and we started using PET's in radiation therapy about five or six years ago and what we've done, we had a separate PET scanner we would get images on a PET scanner and a CT scanner, fuse them, and then use them for treatment planning. Late advent has been a PET/CT scanner where PET scanner and a CT scanner now share a common housing; they are sort of "duct-taped" to each other, but they're still two separate gantry's, but they live in the same shell, and I will talk about it in a minute. But, still sort of to address the issue of probably what the majority of you, many of you can have, is have a separate scanner on a PET site and on a CT site and how do you bring the images in.

Well, like I said, there's a fairly small amount anatomical information that can be easily recognizable on CT and PET and the registration either can be automatic if somebody used multimodality mutual infor…no, maximizing mutual information algorithms that allows for good registration; also fiducial markers allow for very good registration, but I think, there's a talk on registration later on this day…today, so I won't go into huge details, but basically, we have software registration or we have hardware registration. Software registration is where you have two separate scanners and then you use software tools to somehow fuse these images; and hardware registration is, basically, both sets of images are acquired on a same scanner and they're registered by virtue of…by virtue of scanner geometry. One of the things that we've done to be able to do software registration and incorporate images from two separate scanners is use

fiducial markers. We use microcentrifuge cubes that are used for biology or chemistry. They're basically .5 cm in diameter, 3.5 cm long, for CT with secure subliminal wire at the tip of the ampule. For PET, we put a small drop of FTG at the very tip and then the surface tension force holds the FTG in place and then we have marker…we have holders that will allow us to attach these fiducial markers through patient and then from one imaging modality to another, we'll just slide the fiducial marker out and insert appropriate marker for that imaging modality, and we can also use these for MR with some copper sulfate or copper nitrate inside. So, basically, what happens on PET image the markers will balloon, they will always show larger than what their real size is, and as long as you find the center of mass or the center of the sphere, you can pinpoint where the origin of radioisotope is and then you would come to the CT, find the location

of the wires on the CT image, and co-register images using fiducial markers and we typically get a very good registration. Now, one of the limitations of stand-alone PET scanners is a very small bore opening. Typically, these scanners have 55-60 cm bore opening compared to 70 cm bore opening of most conventional scanners, so it severely limits the size of the patients that we can scan in a treatment position. This is an alpha cradle for patient that weighs, I think, about 150 pounds, a fairly small patient and you can see that the alpha cradle barely fits through the gantry. Another thing that one would want to get from a PET scanner, if you want to use a stand-alone PET scanner, you would like to have a flat table top similar to a CT simulator and also external lasers, which greatly improve patient positioning. So, we now have, I think, three PET scanners in our place that have flat table tops and external lasers and it's…the **patient's producability**

from CT scan to PET scan is fairly good, but the gantry bore size continues to be the major limitation. Also, another limitation of a single…of a stand-alone PET scanner is a fairly long scan time. It takes about 45 minutes to scan a patient. There are two scans: one is the emission scan, which we actually use for the treatment planning; and there's a transmission scan; which is basically used to measure patient attenuation properties…radiation attenuation properties, and, due to the fact that we have to acquire two scans which are both fairly lengthy scans, the overall scan time is long, and, again, I won't go into great details because there have been other talks here that discuss this much…in much greater detail, but **(--?--)** mass is a fairly long scan time and the patient does move during the scan. Now, and I mentioned, or I alluded before to a PET/CT machine where two units are housed in the same plastic shell and they share a same

treatment table. The multislice CT, one of the advantages is it's a faster scan time. The CT image of the CT scan is used for attenuation correction factors so what happens, CT is much faster in acquiring attenuation correction factors than stand-alone PET scanners, so there's a significant amount in time reduction due to that; also there's an improved image quality. The attenuation correction factors are much less noisy if they're measured with CT than if they used…using polystyrene emission and transmission scans on a stand-alone PET scanner, and another advantage of a PET/CT scanner is that images are registered in hardware because the patient is on the same scanner, in the same position, and the CT scanner and PET scanner share the same image matrix when you have the images acquired on the scanner they are automatically registered. Typically what happens for radiation oncology purposes, at least what we do, we

acquire three scans: one is the attenuation correction CT, which is typically a low mA, thick slice, whole-body scan and that's used for PET image reconstruction, we will then acquire PET scan, and then, finally, we will get a treatment planning CT, which is typically acquired over the tumor volume with thinner slices and also with contrast. And you have to give a contrast following the PET scan, or following actually the attenuation correction CT, otherwise the PET reconstruction data would be incorrect. One of the limitations still of a combined PET/CT scanners is that CT and PET bore openings is not the same for both imaging modalities, and that's not actually true of all manufacturers. For example, this is the scanner that we have and this scanner does have 70 cm opening all the way through, CT and PET have 70 cm bore opening, but other manufacturers have, for example, 70 cm CT opening, but then the PET scanner will be down to 60 or 63 cm and, again, limiting the treatment position or the scan position for radiotherapy patients. Now, just because a patient is in the same scanner, in the same

position, does not necessarily mean that we have a perfect registration. This is one of the first patients that we scanned and in the background is a Gy scale CT image and overlay is a PET image. So, for example, if you concentrate on this kidney, you can see that there's a shadow on the CT and that there's uptake in a kidney of FTG, and there's actually fairly good registration. But, then, as we scroll through these images, eventually the CT will not show kidney any more, the kidney has disappeared on CT; however, it's still there on PET image, and, as we go on, the uptake will disappear from a kidney and we will have kidney analogy and on the CT, and a similar happens with the rest of the anatomy in this patient. So, there are a couple of reasons for this. One possibility is the patient moved between the CT acquisition and the PET acquisition, which would…which would make a fairly poor registration; also, it would degrade the PET

quality. Another option is that actually the patient breathes and this is what is more likely and as the patient has internal motion, we cannot get a good registration between CT and PET, and this is where the formal registration or 4D-CT or 4D-PET, where we reconstruct both sets of images to a common time frame and register anatomy as a function of time will come in place; and, I think, very soon, in the next two years, just as we have the 4D-CT talks, there will be 4D-PET discussion and what I've shown will probably become less of an issue, and it will also improve PET image quality. If we can have a better temporary resolution in PET, we may be able to detect smaller lesions with a smaller uptake. Now, one of the great disadvantages of PET for radiation therapy, at least up to this part, has been staging. We know that local regional progressions…progression after course of therapy means that we probably did not truly

appreciate the extent of the disease and we did not treat appropriate volumes. Also, we know that staging…true staging is most…in most situations the best indicator of patient survival and the outcomes. So, what PET does, it hopefully allows to better appreciate the local regional extent of the tumor and also appreciates the true extent and it has been shown to do this for lung, for GYN, for colorectal, and so on, and I think, like we discussed before, truer stage will help us treat the patient more appropriately. Now some of the examples of where PET has made actually a difference in staging, one of the largest groups…largest studies came out of Australia and was published in *Cancer* a couple of years ago where they looked at 153 patients prospectively with a non-small cell lung cancer and they looked at the before PET stage and after PET stage and they also looked at the subsequent patient management and survival. Well, after the PET stage are

strongly correlated with the two-year survival indicating that PET is a very good indicator of how these patients will do and it did much better than CT. Another thing that happened in this study is that roughly 20% of the patients were upstaged due to PET information and they were actually treated differently; five patients actually were downstaged, and about one-third of the patients that actually were curatively treated, you know, if you exclude the 20% of these five patients, you're left with 102 patients and about a third of them had a change in volumes. The volumes were either increased or decreased compared to CT data by using PET information, and another study which backed up this information came out of Toronto-Sunnybrook **(--?--)** colleagues looked at a small group of patients, three patients, but roughly, again, about 20% of their patients were upstaged and then, again, significant portion of the patients had the change in

target volume. In **Kati's** paper, actually they have a range because they had different physicians contour tumor volumes and depending which physician contoured, there was a difference in change, and I will talk about why this range is and what is the actual problem of contouring with PET. Another study that happened and was published in *Journal of Nuclear Medicine*, is they did a study or did a survey of referring physicians in how PET information influences patient management and they looked at 202 patients across different treatment sites and roughly one-third of those patients had a change in treatment management due to PET information. They either had a change in target volumes in intensive therapy or actually in dose that was delivered to these patients, and this is why I say that functional information and multimodality information has a very strong potential to influence what we do, and we may not necessarily see it in daily

operations, but the referring physicians certainly do change the pattern of what is being referred to us. Now, one of the things that one is to be careful when incorporating new information in clinic, is to avoid false positives or false negatives or **unwarrantedly** change the patients' treatment. I think this technology has to be implemented with the grain of salt and certainly have to validate clinically any changes or justify them clinically prior to affecting patient outcomes. And, I think these studies that will validate or that justify the import of multimodality information and change in treatment need to happen in order to do this correctly. And one of the examples, for example, is if you just go on contour PET volumes, what you see on PET may not be true. For example, if you look at this PET image, this is a patient with a thorax tumor, well the **window** level and the size of the tumor actually seem okay; many people, you know, wouldn't

argue this is inappropriate. However, if you change **window** level just a little bit, you, again, have another image that looks reasonable; however, the size of the target or the size that you would **dose plan** on PET is substantially different and there are a number of people who are working on solving this problem; but, nonetheless, it is one of the issues that we have depending on **window** level, we see different things on PET and one needs to understand how to find the true extent of the tumor. One of the things that was proposed by **use of verde** is to use the threshold technique where one finds the maximum intensity in the tumor and then go to a certain percent of this maximum uptake and contour that as the extent, and, typically, people refer to about 40% as correlating well with the edge of the tumor. However, there have been a number now of studies that are questioning these numbers and saying that this may be done better. One

of the things that we can do is actually use respiratory gating or 4D-PET and take out the motion out of the PET images and, hopefully, find better the true shape of the tumor and correlate that better to the CT images and also be able to use the SUV's to contour the target volumes. I won't go into great detail about this, but one option is to have the 4D-CT's. On the other side, there's a group or at least one paper that suggested that free breathing on PET actually **trenosus** where the tumor goes as a function of time and may be used better to contour the PTV is because if you see it on a PET means that that's where the tumor went during the free breathing cycle for a long period of time. One of the things that we've been working on, and I'll sort of try to wrap up in the next few minutes, is couple of studies and we have actually changed some things so see if we can actually use PET information for the treatment planning. So, one of the first things that we've done to see if we can PET images to delineate cervical cancer tumor volumes and then use that information also to plan brachytherapy implants. So, basically, what we do, we take a patient

to the OR, we insert a **tandem and copple stats** and then we take the patient to the PET scanner and we insert tubes containing FTG into the **copple stats and to a tandum** and at the end what we get is a PET image that shows us where **copple stats** are or where the applicators are, we can see the bladder, this is a Foley catheter, we can see the rectum. Well, if we can see the bladder, we can see the rectum, we can see the **copple stats**, now we have **critical** structures, we have the sources, and then PET, of course, shows the tumor and we can calculate those distributions and actually see how much radiation we give them from brachytherapy implants from the PET information, and then we have three-dimentional dose distributions showing us what actually is delivering…being delivered to the PET tumor volume. But, more importantly, we can actually re-optomize what we're delivering. The way that we deliver brachytherapy, we have point A

dose, which really does not correlate to the true extent, or size, or shape of the tumor; and brachytherapy, historically, has…or cervical cancer brachytherapy has not been tumor-volume based, rather it's been based on point A dose of milligram hours. Well, this is a study where we take same milligram hours with same loading in the tumor, but we distribute the source position to conform better to the target **distent**, and, hopefully, if we do this we may have a better control. Now, one of the things is that we haven't done this because we have very good outcomes with this technique and we're afraid that, you know, enemy of good is better and if we change to maybe to modify what we've been doing historically, we may not have as good outcomes. Another thing that we've looked at is possibly to use PET information for treatment of patients with cervical cancer who have para-aortic involvement. We know that these patients do very

poorly. There have been a couple of RTGO studies that have shown that if you actually treat para-aortic lymph nodes that these patients do have a better survival; however, the dose is limited to 45 Gy because of proximity of cervical structures. You know, para-aoric lymph nodes are surrounded by spine, by bladder, by kidneys, by intestines and giving more than 45 Gy with conventional delivery techniques is fairly difficult, so what we try to do is use PET to identify positive lymph nodes and then use IMRT to deliver higher doses to these volumes. So, basically, what we have is two treatment areas within the patient. The pelvic region…or a…or the pelvis is typically treated to by 50.4 Gy in combination with brachytherapy, and then the para-aoric region is often treated to 45 Gy, again because of the proximity of critical structures. In our treatment technique, we use the same method. We still have two separate regions—we have a pelvis and

we have para-aoric region. The pelvis we treat still with APPA or right left lateral to 50.4 Gy and we still have a brachytherapy boost, because we have a very good survival and very good control in this volume, so we want to leave that unchanged using conventional therapy treatment techniques; but then the para-aoric volume we treat with IMRT. So, what we do, we put central axis at L4-L5 into vertebral body space and, basically, close the upper jaw when we treat the pelvic and treat the pelvic with the lower jaw; then when it comes to the IMRT, we close the lower jaw, open the upper jaw and use the **MLC's** to deliver radiation to the upper portion of the field. And, basically, the way that the process goes, we have a PET scan. On the PET scan, we identify the lymph nodes with the uptake, we map those lymph nodes to a CT scan, and then we use IMRT to deliver escalated dose to those lymph nodes. This is the first patient that we've

actually clinically treated. We delivered 6000 cGy to the positive para-aoric lymph node, and at the same time we delivered 5000, which is a little bit higher than 45 Gy, to the para-aortic lymph node bed while keeping doses to critical structures to acceptable levels. Now, this is one of the sites where we felt it was justifiable to treat what we have done conventionally. We know that these patients have poor outcome. We know now where these…at least we think that we know where the disease is, and we felt that we can deliver radiation safely without great chance in reducing the conventional outcomes. So, we felt that this was justifiable to actually go ahead and modify the treatment based on multimodality information. So, I think, in conclusion, biological imaging will definitely allow us to treat patients as individuals and have individual plans, rather than have the statistical approach to decision…to the treatment…to the treatment sta…to

decisions. CT will remain the cornerstone due to its image…due to its spatial resolution, due to the information that it contains for **hydrogenating** calculations, and ease of access. However, I think the current practice of radiation therapy will change because of the imaging modality. We will certainly re-evaluate past clinical trials because it's possible that a lot of trials that we've done in the past that have failed to show benefit, actually had a substantial portion of the patients who had a more advanced disease and these patients probably have affected the outcome of these trials and the trials may be…would have been successful or would have shown benefit had the patients been appropriately staged and then, I think, we will have different treatment techniques or treatment approach as the multimodality information gets incorporated in the clinic. And, I would like to thank you for attention.