

Thank you very much, Bruce, for that introduction. In fact, the number is over 400 PET/CT scanners out there. And what I'm going to do in the next 25 minutes or so is just briefly describe the initial concept and then take you through the current status of combined PET/CT instrumentation, mention a couple of the issues with respect to the protocols and the use of PET/CTs in the clinic and then end up with an image or two from our 16 slice LSO PET/CT at the University of Tennessee Cancer Center in Knoxville. Why multi-modality imaging with PET/CT, or indeed with anything else? Obviously we're imaging complementary aspects of disease. The devices we've put together, and PET/CT is obviously technologically less challenging than PET/MR, the goal is to image different aspects of disease that are complementary so you end up getting more by imaging the two than by imaging them separately.

Also, as we've progressively understood, the combined PET/CT scanner increases the accuracy and confidence of interpretation. In a statement made by a colleague of mine from the University of Pittsburgh, a world-renowned abdominal CT expert, he told me that one of the things he'd been amazed about with the PET/CT is how much, after 20 years of reading CT, it had taught him about CT having the complementary functional imaging information. And another major importance of dual-modality imaging is to compensate for the non-specificity of probes. Clif has just described very nicely the use of hypoxic imaging probes which are very specific to certain types of cells, particularly the cells within the tumor. However, the most widely used tracer, FDG, is highly non-specific. It's taken up in any cell that's metabolizing or utilizing glucose, which includes brain, heart, muscles, and it's excreted through the urinary

system so you get signals in the bladder, in the kidneys, and it's sometimes very difficult, as I'll show you, in the abdominal region to distinguish normal uptake from some specific malignancy. So overall, the idea is to provide some unique additional information as *Time* magazine summarized it very nicely in their article in December 2000, one plus one equals three. In other words, this added value that you don't get by doing the two modalities separately. Of course, we've had fusing of anatomy and function for many, many years, ever since the early days of nuclear medicine when functional imaging of the thyroid. Often the images contained hand-drawn contours to try and make it easier for the physicians to interpret the study. And of course for many years, as was mentioned, the physicians themselves have been doing a visual mental fusion by looking at the two distributions, the two image sets on either separate screens or on the

light box and on a computer screen and visually trying to fuse those images in their brain in order to correlate the various anatomical features with the functional abnormalities. As you know well, there is a huge field of software fusion, the development of algorithms, computer algorithms, that allow you to match certain features automatically according to certain metrics such as mutual information. And to come out with a fused image data set that converges mathematically according to the algorithm. We know this works extremely well in the brain because the brain is a relatively rigid organ within the skull, and at least when you're trying to fuse it or correlate it with images of glucose or flow you get enough anatomical information from the functional image to correlate with the CT, or more usually MR in the case of the brain. In the rest of the body these techniques are often very labor-intensive and often converge only locally

so that certain parts of the body are registered and other parts of the body are not so well

registered. And so in the mid-90's we started to look at the idea of what I call hardware fusion, which is basically fusing the technology rather than fusing the images post-hoc. So the idea is you actually acquire the image, the dual image sets directly in a single imaging device. And when you think about it, it makes a lot of sense given the sort of functional images that we're going to be interpreting. This is a typical FDG, a coronal image of an FDG PET scan and you can clearly see there's a fair amount of anatomical information. This is because of the non-specificity of the probe. There's low uptake in the lungs, there's uptake in some of the muscles, parts of the mediastinum, the heart. And then down here in the abdomen you have uptake in the liver and spleen but also a lot of other activity, areas of elevated or focal uptake and it's clearly difficult to determine whether those are tumoral uptake or whether it's uptake in other structures, normal uptake in bowel or other parts of the abdominal region. And if you look at a transaxial

section there through that level you clearly have a lot of focal uptake and the question is which of that is normal and which of it is not normal. And that was the challenge of the nuclear medicine or PET physician prior to combining this directly in one imaging with the CT. Now CT gives you excellent anatomical localization and most of our cancer patients are still referred with CT scans to our unit, not MR for the..for whole body imaging. And clearly to be able to correlate those two scans would be much more powerful than looking at the two separately, and when you do that in this particular case you see this area of elevated activity right in the pancreas shown directly on this combined image. I like to think of it as a historical situation that PET and CT have developed completely separately although with a lot of common areas in terms of reconstruction algorithms and so on. And it's been the disciplines that have kept them apart

rather than any good reason not to do the two in the same instrument if you have that technology available. And that was the device that we put together in 1995, and a lot of the ideas were based on the pioneering work in the early '90s of Bruce Hasegawa and his group at UCSF in CT/SPECT who demonstrated the clear superiority of dual modality imaging. We extended it to PET in the mid '90s and put together a Siemens Somatom AR.SP spiral CT technology mid '90s with a rotating PET scanner, which consisted of two banks of BGO block detectors that we mounted on the rear of the assembly of the CT. So the whole thing was a fairly integrated system, and in fact more integrated than any of the current commercial systems as I'll show you in a minute. Apart from the integration of the hardware, the imaging hardware, the rest of the data paths, acquisition and reconstruction were kept separate since we didn't really have access

to combining those systems. So that was the first prototype PET/CT that we began clinical evaluation of at the University of Pittsburgh here in 1998. Based on the 300 or so cancer patients that we scanned on the prototype we generated a lot of interest in combined PET/CT imaging and so from about 2000 or 1999, depending on the vendor, the vendors attacked the problem of how to make this technology generally available to medical institutions. And the basic design approach was to take a standard state-of-the-art PET/CT scanner and modify it either by removing the rear or simply standing it in front of a state-of-the-art PET scanner and, as I said, the level of integration of the imaging systems was fairly minimal. A cover was placed over the whole device so from the user's perspective it looked like one single imaging instrument, but in fact in pretty much all the designs the two imaging systems are kept separate at that level. What

has changed is the integration of some of the acquisition and certainly the computer systems, the reconstruction and display systems that level of integration is much higher than it was in the prototype. The problem with this sort of design of bed is that as the patient carriage translates through the system there's a vertical deflection of the carriage caused by the weight of the patient and the anchor point or the lever arm effect on the bed, and this is undesirable in a dual modality system because in a single modality system once the patients pass through the imaging field you don't really mind what happens afterwards. In this case, if the patient bed starts to sag downward then that's obviously going to lead to a misregistration of the two image sets. So the design that was implemented in the system that I helped develop was to take away this variable cantilever point, just fix the bed here and then have this whole..this whole assembly translate, so

once the patient is lying on the bed, and some of these patients that we image have weights up to 400 pounds or more, the vertical deflection is fixed and there's no further deflection as the bed moves through the tunnel. So this was an important design feature in the commercial systems. And what we've seen is as I'll show in a minute, there's been a progression from one generation to the next, it always combined the very top end CT, so although our initial systems are 30 rpm, now you're seeing PET/CTs with up to 16 slice CTs with rotation times down to .4 seconds, so usually state of the art multi-slice CT with the really top end PET. And this is indeed the various designs that we've have over the last three years and it's hard to believe that the first commercial system to appear, at least the one in the US was the Discovery LS at Johns Hopkins in early..in Spring of 2001. So in a little over three years there now are over 400 systems out there. The

first systems from Siemens was this biograph classic system that's now been replaced with the 6 and 16 slice LSO multi-slice CT with LSO PET, and that's the one I'll talk about in a little more detail since that's the one we have at UT. The Gemini system is from Philips and this is the..now the latest system that has been out for just over a year from General Electric, the Discovery ST. And at the recent Society of Nuclear Medicine meeting in Philadelphia, Hitachi Medical announced what is really the first mid to low end PET/CT, which is a rotating system like our very first prototype only, based on LSO detectors, not BGO, and a 4-slice Hitachi CT. So this is the first, really the first design to try and impact the mid to low end market which will of course impact the migration of PET into PET/CT since there is still obviously many sites that are not looking for the absolute 16 slice top end multi-slice CT with the very best PET scanner. And

this just shows a table, I won't go through this in detail. It can be available on handout. There are websites that list the various features. These are the CT features and we've seen this progression from the biograph classic which was a single slice CT through the 4 slice, 8 slice, up to 16 slice and plans, as you know, at the RSNA Siemens and GE announced 64 slice CTs, and obviously this is taking PET/CT in the same direction although it's questionable obviously for oncology whether we really need to go even to 16 slice, maybe a 6 slice CT would be adequate for oncology imaging. And on the PET side, there is three different scintillator materials out there in the different PET scanners, different size detectors down to 4 mm detectors in the biograph Sensation 16 that we have. I should just mention this issue of whether..of operation in 2D and 3D since it's been a fairly hotly debated issue. But one thing to draw your attention to is

the switch from using standard PET transmission sources to using CT. And despite the early

intr..in the early systems the provision of both CT and standard PET transmission sources pretty much every site that operates a PET/CT does so using CT-based attenuation correction. Another big important parameter has been the co-scan range which is the distance moved by the patient couch to ensure that even for melanoma patients you can scan from head to feet with both PET and CT which is a challenge for the stroke or travel of the bed given that the two imaging fields are not in the same location, they're often separated by 60 to 80 centimeters and you have to take that into account in the translation of the bed. 3D PET imaging. PET is intrinsically a 3D imaging technique because you inject a radioactive tracer, you cannot collimate that and therefore you're obliged to use..to use the maximum of the radiation, you really need to acquire it fully in 3D. Well, back in 1990 the technique for 3D acquisition in the brain was developed because prior to that for technical reasons PET..multiring PET scanners had these lead septa and

they're basically limiting the acceptance angle of the radiation, so even though the patient received a radioactive dose for every photon that was generated in his body, many of these lines of response were not acquired because of, well, a couple of reasons. One was the 3D reconstruction algorithms were less well developed than 2D reconstruction algorithms. And secondly, in PET imaging you get a lot of scatter, photons that scatter as they leave the body and if you can't correct for them in some way then the other alternative is to just eliminate them with these lead shields. The advantage of 3D is shown here. This is the, if you like, the 2D signal-to-noise curve as a function of increasing activity and this is the 3D curve, and clearly at the sort of..these are the sort of activities we're working with in clinical imaging with FDG. You have a very large factor of signal-to-noise improvement in..without the septa when imaging in 3D. Now

this plot is for a 20-centimeter cylinder phantom, which approximates brain imaging. And indeed, this technology, this 3D methodology was made to work successfully in the brain back in 1990. For the last 11, 12 years we struggled to make that work in 3D for the whole body, and the problem with the whole body is you get much higher levels of scatter and much higher levels of randoms than you do from the brain where you can basically shield the activity outside the field of view. Recently two new..two fast scintillators, this one was developed about ten years ago and this one even longer, in the mid '80s, GSO and LSO. And these new scintillators allow us to operate with much shorter time windows, which significantly reduces these accidental or random rates, and also with much higher discriminator levels that allow us to eliminate or reduce the scatter background. So the introduction of these faster scintillators, this is the one that Philips

uses, this is the one used by Siemens primarily. These faster scintillators have helped to make 3D PET imaging feasible throughout the body, both brain and whole body. And the two other reasons why, apart from the new scintillator. One is that we now have accurate scatter correction techniques, these have also been developed. So even though the scatter background has been reduced, the scatter..the correction techniques are much more accurate. And the other aspect that's had a huge impact has been the development or at least making statistical reconstruction algorithms feasible in the clinic, and this is exactly the same data set reconstructed with the 3D reprojection algorithm which is basically filtered back projection in 3D that we've had since 1989, and then these are two of the more recent statistical algorithms, and I emphasize this is the same data set FDG image where you clearly see a uniform liver, spleen, spine and this is all done

with exactly the same data set. So these three factors have helped to make 3D whole body PET imaging work. The major problem that we confront, particularly in the US, is the size of the patient. The average size of our patients in Knoxville will be around about 200 to 220 pounds, and the levels of attenuation and scatter in these sort of patients presents a problem. And the reason for that is that there is a significant degradation of image quality as a function of patient weight. These are two patients right around 100 and 250 pounds, that's the CT. There you can see the much noisier PET image as a result of the increased patient weight. That's the PET/CT image. And there is definitely, as shown by..this is work Eoin Carney in our group, showing a steady degradation of..this is actually the trues, the relative trues rate, trues to total as a function of patient weight and this is about the 70-kilogram level. And many of our patients are sitting up

at this end. Recently new electronics was fitted on our system, which actually gives a better performance as a function of weight. So the two curves I showed you before would be sitting down here, we're now actually getting better performance at these sort of weights but at the upper scale, the upper end, there are still issues with patient weight simply because of the huge amount of attenuation. So this is the major, when people say how long do you image for, now when patients are scheduled the weight and height of the patient is two of the most important parameters to note so you can schedule a scan time of..appropriately. I'm not going to go into this in a lot of detail because Eoin Carney will present at 7:30 tomorrow for those of you who get up at that time, more details of the use of these CT images for attenuation correction, but the main point to note is that what we're doing in PET transmission imaging is just a CT scan at 511

keV. We obviously have a CT scan at 70 or 80 keV, and if you look at the ratio of the attenuation factors as a function of Hounsfield units, you can see that fortunately a lot of the tissues, lung, fat, many other tissue, soft tissues, have pretty much a single value for this ratio so you can just take a single scaling factor and scale the CT image at 80 keV up to 511 keV. Bone is a little bit more complicated. As you can see, there isn't a single factor but since the number of bone pixels in a typical image is relatively small, most algorithms actually put a breakpoint somewhere around zero or a little bit higher Hounsfield units, and then scale all tissues below that value with one constant and then all tissues above that, making a small error with some of these bone pixels. It is very difficult to demonstrate whether that has any effect. So our CT-based attenuation correction algorithm that Eoin will describe in more detail tomorrow is to

segment into soft tissue and bone and then scale the bone using, as you can see here, the bone values are little different from the soft tissue, at least at the CT energies, that's why you use those energies for CT to get that contrast. You have those two scaling factors, and you end up with a scaled CT image from which you can generate your PET attenuation correction factors. There's two issues which have affected the use of CT-based attenuation correction. One is the mismatch of respiration between the CT and the PET, and the other is the use of intravenous or oral contrast in the CT. There's a number of protocols that are being developed, breathing, different breathing protocols but as we move to the high speed CT with less than 10 seconds for a complete thorax requiring the patient to hold their breath not at full inspiration but at partial inspiration is now feasible, and by gating, and this is another thing that we're learning from radiation therapy, to gate the PET image we can select a frame in the PET image that almost

exactly matches the CT. And there's a lot of work going on at MD Anderson and Memorial to address these issues. The second issue is whether or not you give oral contrast and we systematically give oral contrast. We also give IV where indicated in head and neck. Oral contrast, barium sulfate in the stomach, the Hounsfield unit level is about 200, Hounsfield units enhancement. This increases as the contrast moves through the gastrointestinal tract into the lower part of the abdomen, increasing up to about 700 Hounsfield units, and the problem is that if you put a threshold somewhere these pixels will be scaled as if they were bone because they're enhanced and appear like bone on the segmented image and you don't want to scale them as bone because you can potentially generate focal areas in the..in the PET image when you apply the attenuation correction factors. So Eoin Carney developed a technique to distinguish the bone pixels from contrast. To do this, the first thing is to extract the bone and the way that is done is

by a region-growing technique where the seeds are the cortical bone pixels which are very easy to segment because they're very high values, and that way you can actually segment out the skeleton and remove it from the CT images. So as each bed position, as the bed moves through the PET scanner, as each bed position is completed, these factors can be applied since the CT is done first. And then at the end of the PET imaging it's just the last bed position that needs to be reconstructed and then a fused image can be formed directly within a couple of minutes of the completion of the scan. Some of the advantages now to finish up with so I can show you a few images from some recent PET/CT cases. This is a typical, it happened to be an incidental finding in a patient where they thought there was some problem of cervical nodes reported on CT. This is an incidental finding in the pelvis and normally this would be very difficult to

determine where this obviously foci elevated uptake is actually localized, but when that's the corresponding CT section and when you put the two together and see this exactly localizing within the colon in this structure, the patient has undergone a colonoscopy and we're still waiting for the report as to whether that was a precancerous polyp or actually the development of malignant disease. But that would be very difficult to localize without combined PET/CT. I wanted to emphasize one other point that goes back a little bit to what Clif Ling was talking about in terms of spatial resolution. There has been tremendous progress in improved spatial resolution very recently in PET imaging. And this, you might have seen this article in *Fortune* magazine in March of this year showing the 5-year survival over the last 30 years or so in the four major types of cancer. As you can see, lung remains still a fairly miserable 5-year survival,

but these are patients with localized disease so no metastatic disease on staging, but when you add to that the progress over the last 30 years for patients with distant or disseminated disease, you can see that there's really, and this was emphasized in this article, very little progress indeed in terms of the 5-year survival over quite a range of effort in terms of attacking this disease. So the key is to get it early, I think Clif said that, and that means detecting smaller and smaller lesions. And so what I wanted to finish with is to show you three cases of where progress in detecting very small nodes and the key is to be able to recover enough activity in lymph nodes or small lesions that are below the level at which they become positive on CT which can often represent a fairly advanced stage of disease. This is a patient with stomach, initially with stomach cancer. And she, the patient, she was being staged and what we detected in the

mediastinal region are these lymph nodes here that were positive, peri aortic lymph nodes that were in the range of 3 to 8 mm in size. Now this does not mean that we're getting full activity recovery from these nodes but the resolution of our system is 4 mm, which may be 5 or 6 clinically, but we're getting enough recovery to be able to identify nodes that are negative on CT. So this has been a big..our system was upgraded in November to the 4 mm detectors and there you see a node, this is in the 3 to 8 mm range, below the level for CT. And a lung cancer case, restaging lung cancer in a 67-year old male and here you can see all of the vessels and this lung window but there are two small nodes in the lung. The one on the left is an 8 mm node and the one on the right is 3.5 mm. And they were positive on PET/CT, as you can see there. This node is, as I said, about 6 by 8 mm with an SUV of 6, and this node is only 3.5 mm, SUV of 3.1. And

this is a big step forward in trying to diagnose disease at an earlier..diagnose and stage disease at an earlier..earlier in the progression of the disease. And finally this, Cliff mentioned imaging with hypoxia. We are doing some..these are fluoride bone images. I think the power of this technique will be to go to different probes. Hypoxia was mentioned. This is fluoride bone imaging looking at the metabolism of the bone. This is a patient with metastatic breast cancer. This is the sort of image quality you can now get with these high resolution systems, and you can see metastatic disease in the pelvic area, in the skull and in the spine. So this is the latest stage of that. It has a 70 cm patient bore so we are using it also with lasers, Lap lasers in the imaging room for radiation therapy treatment to at least imaging the patients in the radiation therapy position. And as I mentioned, with the elimination of the transmission scan, the scan time has

dropped dramatically from the 40 or 50 minutes we had about four or five years ago is steady progression down to now these fast LSO PET/CTs where you can image at last in reasonable sized patients down to as little as 10 minutes or less per scan. And the..this shows, my final slide, the adoption of PET/CT in the last..since 2001 when the very first commercial machines appeared the steady progression representing now about 80% of the PET market. And I think to take it further, there is going to be a need for a system like the Hitachi system with a midrange PET instrumentation with 4 or maybe 8 slice CT. So I hope this has given you some feeling for the rapid development of this dual modality imaging technology. And I thank you for your attention.