

Thanks very much again Stan, for a chance to be here. It's always a pleasure, and I'll review first of all what we talked about last year. You can see last year's agenda for this section of the talk, and it was mostly favorably reviewed, I think, except for one comment that I can't help but remember. I've tried not to take that too personally, but I did try to adapt the talk this year to a bit more question-driven and practical focus. So let's just see what if we can talk about three simple questions and address them at least from a conceptual standpoint with some amount of actual data to support some—if not answers—frameworks for answers. What happens inside and outside tumor and normal cells after stereotactic body radiation therapy? What normal tissue radiation dose constraints should we use in this field? And, finally, what radiation doses should we try to give to tumors using SBRT? Let's consider these questions...First, what happens inside and outside tumor and normal cells after stereotactic body radiotherapy? You could think

of it in terms of at the subcellular level things that go on, at the cellular level, and at the sort of tissue level. Looking at the cellular level there are a host of repair signals and pro-proliferative signals that serve as a defense mechanism for a cell that's received radiotherapy. They are often mediated by cellular growth factor receptor events, and they are shown in diagrams like this, of which I'm not trying to make an eye chart...but in fact I think this is the part that's too much biology, because in fact even... professional card-carrying radiobiologists have trouble keeping track of the myriad and very complex pathways and chain-linking domino effects that go on in cascading cytokine effects inside of cells. I'd say you could probably keep track of perhaps a few of the key ones, because there are a few agents out there on the market and in late-phase clinical testing which are able to impact important pathways. The ones I'm thinking of, of course, would be the agents which affect the EGFR-mediated signaling. Those would

include Erbitux®, an antibody-based therapy, Iressa®, and a host of other agents designed to impact signaling that begins, or is at least transmitted through, surface-bound receptors, but in any case I think an awareness of this, an awareness of the ever changing nature of this, an awareness of the fact that there are many people studying these pathways and seeking to influence them by targeting specific points along the way is probably the key thing. I should mention that at the cellular level there is, of course, both DNA injury-mediated clonogenic cell death, which produces what's called the reproductive sterilization, if you will, a very traditionally well understood form of killing off a cancer or normal tissue cell, and, of course, apoptotic cell death we'll talk more in a moment. And then again at the tissue level there are messenger molecules also known as cytokines which are expressed in some fashion. Consider just this issue of clonogenic cell death and apoptotic cell death: naturally in tumor tissue the more, the better.

We'd like to kill as many cancer cells as possible; we'll take it whether or not they're killed in a reproductive fashion with traditional DNA mediated injury or whether they are sent into so called program cell death or apoptotic cell death. Probably the majority of the cell killing is done by DNA injury-mediated death, but there is a not insubstantial component of apoptotic cell death. It's probably, it's been advanced at least hypothetically that in normal tissues the apoptotic component might be an even more important consideration than the DNA mediated damage. I show here some slides from Paul Okunieff which are trying to illustrate a certain point and that is that if you can imagine radiation in the sense, in this setting hitting normal tissue cells and causing perhaps some injury that is not necessarily manifest at the first cell division, but

ultimately winds up apoptotic cell death that is triggered and causes a depopulation of a substantial component of that normal tissue structure. You can imagine the possibility of severe normal

tissue toxicity as a late event. If cells and normal tissues are “reproductively sterilized”, but are slowly dividing cells that don’t actually express that type of damage and go on to continue with their function, you might not get nearly so much end organ damage. Now just to consider this other topic of so-called messenger molecules or cytokines that are expressed, I’ll show one example of what that looks like in the raw data form and comment on this particular individual’s results. We’re beginning to look at this... issue in a study we have ongoing, where we will obtain blood samples before radiotherapy immediately after, and then 30 days after stereotactic body radiation therapy. Among the ways looking at them is with what’s called a cytokine array. This particular grid you see here represents a plate on which there are antibodies, which will bind a number of known important messenger molecules, or cytokines. There’s also a lane here for a control protein so that all the results can be more or less normalized. The more protein that’s

expressed, the more protein that’s in the serum you’ve obtained, the more that will stick to this plate and will be counter-stained if you will, with an autoradiographic method. In this particular example, I’ll share with you the one most interesting result, which is the fact that there appears to be an increased expression of something called VEGF, Vascular Endothelial Growth Factor. This is perhaps interesting because not only is it well known as an influence upon angiogenic effects--one of the tumor’s other defense mechanisms for survival is to produce new blood vessels which will supply and nourish additional growth—it’s interesting to note that this is expressed in this setting because there are also agents which can influence VEGF, or at least bind to it, and inhibit its activity, so I think that the study of patterns like this, although they do become a bit difficult to stare at in this format at a meeting presentation, may actually lead to some practical information and some understanding of events which happen that can be

influenced and targeted and may prove advantageous therapeutically. Let’s consider the the second question: what normal tissue radiation dose constraints should we use in stereotactic body radiotherapy? We’ll comment first of all on the parameters that have been advanced for lung tissue in the RTOG 0236 study. I’ll comment on liver in terms of expected radiographic changes that you will see, and also something we’ve applied, which is a modification of the so-called critical volume model, and then I’ll say a few words about the spine. This RTOG study that’s been mentioned now twice by Stan and myself is a phase two trial of stereotactic body radiation therapy in the treatment of patients with medically inoperable Stage I and II non-small cell lung cancer. PI, Robert Timberman, who is now at the University of Texas Southwestern. Eligibility will include patients who have small, medically inoperable non-small cell lung cancers. It is allowable to have a T3 tumor which is a chest wall primary only. It’s not allowable to have a

T3 tumor that’s defined as T3 by virtue of it’s central location. One of the exclusion criteria is, in essence, a normal tissue consideration, and that is that no patients with tumor of any T stage in the zone of the proximal bronchial tree are allowed. I’ll show you a picture of what that means. And the dose fractionation established from the prior work at Indiana University, the phase one dose escalation study, is the choice of 20, is 20 Gray per fraction for three fractions. Now let’s just look at the individual specifications and make a comment or two. I mentioned that written

into the eligibility criteria, or exclusion criteria if you will, is an exclusion of patients who have tumors in the zone of the proximal bronchial tree. You will see in your protocol copy a sketch of this proximal bronchial tree. What you see here is the trachea dividing into the two mainstem bronchi and then an outline of a two centimeter margin around what is considered to be the proximal bronchial tree. Now, the reason for this particular exclusion criterion

has to do with an early observation or two at Indiana University of the possibility that there might be an important serial component as opposed to just parallel component to lung tissue tolerance. I think most of us understand the lung parenchyma as being more or less a parallel structure. There is a certain amount that you can lose and spare and ... most of us go around with, fortunately, plenty of that to spare. It is possible that if you had fibrosis selectively localized at one of the larger airways more proximally; you could get some risk of collapse. Now, I say that I'm taking this (with a grain of salt)—certainly we intend to try to put people with protocol and with respect to this criteria, I'm not totally convinced that this is an actual phenomena or might not have been idiosyncratic observation or two, perhaps even just from tumor progression. We've not seen this particular problem, and I don't believe too many other investigators have seen this problem and when the Indiana University folks tried to replicate it in the lab they were actually

unable to replicate this particular phenomenon with an animal model. Having said that, certainly the first protocol going out into the group setting should err on the side of caution so I would not speak against this particular eligibility except to say that maybe it is and maybe it isn't part of being over cautious. Target dose specifications. They're going to allow a certain amount of inhomogeneity. I believe the range is the requirement for the prescription dose to be between 60 and 90% of the maximum isodose line. There happens also to be a requirement for "isotropicity," if you will, of the dose distribution. You are required to achieve a dose fall-off to within about 50% of the prescription dose by 2 cm of the PTV. Now, I say it's about 50% because there is a size-dependent limitation on that. There's a table included in the protocol. And I think the point of this is partly to respond again to the issue of being concerned about not giving too much dose to proximal airways where damage might cost you more than it does peripherally,

and I think it's also a generalized restriction on having an awareness of the importance of limiting dose to the remainder of the lung. There is a so-called V20 requirement. V20, as all of you know I'm sure, is the percent of normal lung tissue receiving above 20 Gray. In most conventionally fractionated protocols, if you read the fine print, the restriction on that number would be in the range of 30-35%. In this setting we're restricting it to something less than 10%. I think with a good stereotactic system, it's not a problem to do this, but, ...again, this...percentage has been sort of scaled down in consideration of the high doses that are given to the tumors. There are, of course, some spinal cord, heart, and esophagus limits also built in. Apropos of nothing except the fact that you're suppose to show a little show and tell, I'll just mention that in fact we have the Novalis® system when we do our treatments. Here you can see from

this company website photo that there is the option for yellow x-rays, if you want, in your orthogonals. We ordered the blue x-rays for our center. We just thought it would match more. But, in any case, you can know that when, those of you who have this system [that was a joke!]. Those of you who have this system, know that the system involves registering DRR's, obtaining orthogonal x-rays and infusing them for the purpose of defining how many millimeter shift there ought to be to match the setup that you have with the setup that's intended. We've added to that something we call the CERTAIN® technology. We hope to get very rich on this. It's called the Colorado External Registration Thing And Instant Notifier. ... We found that in fact with small field views of the ribs, I'll tell you what was driving us crazy, was that with more or less parallel ribs, we are always afraid that we were one ribs, entire rib space off and it just drove us crazy. So, we've taken to putting a little twisted wire like that at the time of the simulation and

putting a tattoo on it and putting that same thing on it to set up, and at least we feel somewhat more relaxed about not being an entire rib space off as we're trying to be, you know, within sub-millimeter, within a few millimeters of accuracy. We'll be...selling these things. The raw material for this costs \$.50 but since we're going to verify its radio-opaque characteristics, we'll be selling them for \$3,000. The German group: I say the German group broadly speaking, there're folks in Heidelberg and folks in some of the other major German universities who've really gone far in the study of this technology in liver tumors and have put a number of good papers out in the Red Journal already on this topic, and have in particular studied and characterized the expected normal tissue reactions you'll see in the liver after stereotactic body radiotherapy. They've characterized really Type 1, Type 2 and Type 3 reactions. I think there's an important issue of need-to-know awareness here in the sense that the liver is probably trickier

to analyze after this type of treatment because you will get an edema zone around the tumor and there's going to be the frequent reporting from diagnostic radiologists not necessarily as familiar with this in terms of characterizing follow-up scans as showing enlargement of the tumor—when in fact you're probably seeing just a reaction, an inflammatory reaction, or an edema zone around a tumor. Again, just for a sort of useful descriptive terminology, a Type 1, Type 2, and Type 3 reaction have been advanced. The Type 1 reaction is a hypodensity, and I think that's more of an edema-like reaction. Type 2, which happens a little bit later, you get a little bit reduced density and start to see a little bit of contrast enhancement and Type 3, is a sort of combination thereafter. Let me just show you an example. A so-called Type 1 reaction, again if you would say that this is the treatment area, in this case an example of a single fraction treatment... I think, however, you're going to see the same thing if you used a hypo fractionated

treatment. In this high dose region six weeks or so after treatment you will get, like I say call it an edema zone—call it what you want—but around the actual growth disease a change very graphically which easily can be mistaken or have similar appearance to an enlargement of the tumor. I think that's the main cautionary note. A bit later this change will tend to consolidate and shrink a little bit and even become a little bit more contrast-enhancing, and again the observation is that over time after radiotherapy, that so-called Type 1 reaction is going to appear first. The overall volume of the effected area that's just showing scar tissue or delayed effect is going to shrink over time. We have had a multi-institutional Phase 2 study of liver tumors ongoing, and we approach this issue of liver toxicity from what I suppose would be called a variation of the critical volume model. The critical volume model, I think first advanced by a

fellow named Yaes a while back, is the notion that there is in certain tissues a requirement for a certain amount of it to be preserved in good functioning order. It's easy to find surgical literature that would document that

patients can undergo fairly extensive resection of huge chunks of liver—you can probably get 70 or 80 percent of the typical liver resected and still have enough recovery. So we approached it in the same sense that what we ought to be doing here is, at least, preserving a certain amount, or certain volume of liver—no matter what we do to the rest of it, that we ought to preserve that. And we... based on surgical reports estimated that a very conservative estimate would be to say that if 700 cc of uninvolved liver received a dose not expected to cause injury or damage to the function of the tissue, then we ought to be safe, and we'll be... It turns out you can do this and you can escalate the dose pretty high and we'll actually present some of this data ASTRO. As far as the spine, I did mention it as the third consideration. I would say that's probably number three in the list of extracranial locations that folks use. Number four down the list would be I think the retroperitoneal region, adrenal gland, and number five and six, probably

some pelvic tumors, at the moment, at least. I show here an example of a case study provided by the folks at Henry Ford. They're very active in this field of spinal radiosurgery, as are the folks at UCLA, and the folks at Memorial. I'll show you one simple dose -volume histogram that...was provided as an example. In this particular case, the tumor is getting a dose around 18 gray; the chord is being spared reasonably well. I think as a bench mark they would probably say that for a cross section of the chord, no more than 10 percent of it should receive a dose above 10 gray, but I'm really going to stay away from coming down with any kind of firm numerical thing. I think this is an evolving topic. I think there will be investigations which push the traditional limits of understanding of spinal cord tolerance, given that we have a little bit better technology there, and so I want to stay far away from saying what I think is an "established limit" on spinal chord tolerance, because I think it's very much an open and evolving question.

Okay, how much radiation should you give? Now, had we been able to get Danny's slides up first, his would have had a little bit of a background that would set up some of this part of the discussion because he would have shown some dose response data—well, he will show, assuming his slides get up there—he will show some dose response data and also some lung cancer, which form the basis of an analysis offered by the Wisconsin group [Fowler, Tome, and Welsh], to comment on the expectation or at least predictions of response and dose tumor control you'll get from this thing, and I'll show a little bit of our experience to comment on whether the estimates have any bearing on reality. The data that Danny will show will establish that based on actual preclinical data for lung cancer treatment, with the dose of 60-70 gray, you're really going to get a pretty dimly disappointing estimate of progression-free survival at 30 months, assuming no hypoxia. Assuming no tumor hypoxia, dose fractionation scheme which have

been used clinically, are likely to give you a very much higher chance of outcomes, in other words, atypically the 16 Gray per fractions up to 20 Gray per fraction for three fractions is like I give you, under an ideal condition a very high chance of tumor control. The reality is that with the expectation of tumor hypoxia you of course got to modify and down grade your expectations. It is, to summarize, probably necessary to get 20 or 23 gray per fraction if you choose to do a

three fraction regimen to get a very high chance of tumor control. Let me just comment and show very briefly our own, some of our own data. We have two groups of patients, if you will, our retrospective cohort, 93 patients and 114 tumor treated. Most of them in the lung, a fair portion in the liver, and few at the other sites. Tumor volume range is from 0.1 to 185 cc. There is a separate cohort of about 30 or so patients entered on prospective trials—I'll leave those for another day's analysis and just show you our retrospective group prior to the time of using some

dose escalation. We looked at the dose consideration in two ways, by first equivalent uniform dose, and also then by tumor control probability. Many of you are familiar with this particular index. I think it's a very convenient and tidy way of resolving inhomogeneity, and you can account for hot spots, if you will. With that we need to have an SF2 estimate and in tumor control probability you need to add also a clonogen density estimate. The upshot of our observations is that in fact EUD alone is not necessarily predictive of local control. This is our time after stereotactic body radiotherapy and months, six months were getting something about a 75 or so percent control rate, which actually falls off rather disappointingly perhaps down to 50 percent at a year. If you, however, were to include a volume estimate, you'll get a significantly better way of differentiating things. The conclusion from that is I think that size matters, absolutely. It's not just dose, but we're talking about a very wide of range, often, of size of tumors, and so I think it's maybe

as much as anything a proof of principle to see that there is a distinguishing observation between folks treated with a higher tumor control probability estimate, than a lower tumor control probability estimate. I'm not going to say that we've actually come to what would be the ideal dose in that setting. We started off before protocols very gingerly before we began to dose-escalate. I can just say that a dose that might have, you know, 5 or 10 years ago seemed like a very high dose of radiation to give, 3 times 12 Gray to a relatively small tumor, I just can guarantee you it's not enough, if the patient is followed with that, that's a very low likelihood you'll actually control that tumor. I'm going to just wrap up here and acknowledge my colleagues, Tracy Schefter, two students I had working this summer, we have an excellent clinical trials data base manager that has his own venture; we're sort of helping him out. White Dragonfly Ventures Inc. There's his email address. It's been a very helpful tool for us. And I'd like to thank a lot of authors some

of whom may be here, who contributed to a book we have coming out on this topic, which, I hope, covers a lot of these points and then some, also. Thanks very much, and I'll turn it over to Danny now for part two.