

Thanks Brian. Looks like they have us in the correct room now. So just to wrap up I'd like to summarize the clinical rationale and the clinical experience today that has been published so far about this technology. Some of you may recognize LARS Leksell who invented the Gamma Knife and stereotactic radiosurgery and stereotactic radiosurgery was really born of the concept by, that by using precise localization one could better treat the tumor and spare surrounding normal tissues, and just to summarize probably physics 101 for you, in conventional radiation for comparison purposes we outline a GTV, you add a margin to account for possible subclinical spread of disease, which is generally about ten millimeters in diameter and then you add some additional margin to create a PTV to account for movement and setup error, and as all of you know any linear increase in diameter results in an exponential increase in the volume

irradiated. Compare this to radiosurgery where we go with a purely hypothesis that a GTV is roughly equal to CTV, most people that I know doing this do not expand their GTV to create a CTV and then you expand your CTV by minimum margin given the enhanced localization and setup techniques that Stan described, and this results in a significant reduction in the surrounding normal tissue irradiated, and I think one important distinction also between conventional radiation and stereotactic radiosurgery or body stereotactic radiation therapy is that given this reduction and we are able to give either single fraction or hypo-fractionated doses because of the reduction in the normal tissue irradiated. So why pursue this in the body? Well what has been accomplished with the brain stereotactic radiosurgery, we see reduced toxicity from radiation. There is no alternative to surgery that has less morbidity than surgical resection, and there's

also improve tumor control and survival for certain tumors, and so based on this background with brain stereotactic radiosurgery the investigators at Carolyn's Institute, brain stereotactic radiosurgery published their early experience attempting to replicate this type of technique in the body, and they treated. Their initial description was of 31 patients treated to various targets in the liver, lung, and retroperitoneal space. Mean peripheral dose to the PTV was 30 gray and they delivered this in one to four fractions, and the toxicity and the tumor response rates were encouraging enough so that multiple other investigators have begun to look at this treatment. So what are the suitable applications for body stereotactic radiation therapy? Well, I think in general people have gone with the hypothesis that you need a small to moderate volume target. The larger the target in experience from brain radiosurgery we know that, that increases the toxicity.

You don't want to have to try to prophylactically cover areas such as lymph nodes, in patients with lung tumors, because that of course increases your volume significantly. There should be a need to spare radiosensitive normal tissues or a surrounding structure and the normal tissue being irradiated has a parallel architecture such that the functional subunits within the organ can respond and make up for any damage to surrounding functional subunits. Local control is important of course to the overall patient outcome and the dose response relationship should exist. One scenario where these criteria hold true is for patients with early stage non-small cell lung cancer. These patients do not need prophylactic lymph node radiation, and the targets tend to be generally small. So these, this is a summary of the results of conventional radiation for this group of patients. The preferred method of treatment is surgery. The five year overall survival results with radiation are approximately 20-30 percent, and this is inferior to what is seen after

surgery, and this is explained in part because of the patients who are not eligible for surgery had more co-morbidities, however there is probably also a decrease in the control rate with radiation as compared to surgery using conventional radiation, and it has been shown that if you increase the dose that you, this results in increased control rates for this group of patients. However, lung radiation of lung cancer can result in normal tissue toxicity and this is a graph showing both dose responsiveness and volume responsiveness in risk of radiation pneumonitis after treatment. Although radiation pneumonitis is not that commonly seen after patients are treated for Stage I, non-small cell lung cancer. There is a morbidity on the patients, and this is a longitudinal study where patients were assessed for shortness of breath before, during and after treatment, and you can see that the shortness of breath increased for the patients going out to 24 months after

treatment, and this is a group of patients who already mostly have emphysema from long term cigarette use. So this is one group of patients that have been treated by multiple institutions with body stereotactic radiation therapy and you can see that the median follow ups are short, however the local control rates are quite high, and the bottom series is actually a compilation of about 13 institutions in Japan where they collaborated, put their results together and had a 90 percent control rate, and this was presented at Astra last year. So it does appear that we can get excellent control rates in lung and this is again a study that Brian mentioned. The Phase 1 study performed by the investigators at Indiana University, and they treated 37 patients with medically inoperable Stage I non-small cell lung cancer, using the elective body frame with an abdominal compression plate to reduce respiratory motion, and they began their dose escalation at eight gray

per fraction with a total of three fractions, and patients were also stratified by T Stage, which is essentially tumor size, and they reached 20 gray per fraction and did not reach the maximum tolerated dose, and this is the dose that the RTOG study is going to use, 20 gray per fraction based on the Indiana University protocol, and they saw one patient with pneumonitis Grade 3, and one patient with Grade 3 hypoxia out of the 37 treated. And there were six local failures, and they all appeared to occur in patients who receive less than 18 gray per fraction. So as Brian said, some of the lower doses used may not be optimal. How do you compare those doses with what are used in conventional radiation therapy? Well if you look at the top line, they're using the linear quadratic method with an alpha beta of ten. The equivalent dose that Bob Timberman and co-investigators were giving is about 150 gray compared to 60-66 gray with conventional treatment,

and this is the slide that Brian was referring to from Jack Fowler where basically the take home message is that giving 60 gray, if you look in that red line beneath the graph the doses associated, the control rates associated with 60 gray are about 20 percent or the less, and that is right at the bottom of a pretty steep dose response curve, and so if you're giving an equivalent dose of 150 gray you get up into the 70-80 percent control rate range. This does not even take into account the effects of potential doubling time and accelerated population, which are the numbers shown in blue and green, and if you take that into account, the dose response curve may even be steeper. So with these high doses where do the complication rates that people are seeing. Well this again is a summary of various institutions and if you look over to the right, the rate toxicity is generally five percent or less. Now one caveat to this is the bronchial tree that Dr. Kavanagh referred to.

Again, this is kind of an antidotal experience and the RTOG has chosen to avoid treating those

patients with tumors in that location. At MCV we have seen toxicity from patients treated near the bronchial tree and, but I do know again other institutions have not, so this is something that is not yet resolved. This another category of patients that may benefit from treatment with body SRT and that is patients with lung metastases. This is a patient we treated with a soft tissue sarcoma metastatic to the lung. Two years after treatment of the primary no other sites of the disease and the patient was not a candidate for surgical resection, and this is the scan six months after treatment. The patient has done well. There was no acute or late toxicity, and this is very typical response that you will see basically scarring in the area of the tumor, and what is the literature show in results for these patients? Well again the local control rates are high. The series are small but, with longer median follow ups, hopefully we will still see those same high control rates. This is another category of patients who stand to potentially benefit from this

treatment. This is a patient with a liver metastases from colorectal cancer, and this is not an infrequent clinical entity, about 40 thousand per year in the US. These patients are primarily treated with surgery if they are eligible, and most surgeons will operate on patients with either colorectal cancer, or gastric cancer metastatic to the liver, and these are curable patients about 40 percent overall survival at five years after surgical resection, and there are others histologies which also may benefit from aggressive treatment. These are five year overall survivals for different histologies, following surgery, and so there is rationale for treating these patients aggressively and many of these patients however are not eligible for surgery and therefore body stereotactic radiation may be a feasible alternative for these people. This is a graph from the University of Michigan experience showing that these tumors are dose responsive. They see a

significant increase in the control rate with doses above 70 gray, delivered conventional fractionation. But again the liver is an organ that has a parallel structure and there is a liver volume dependence for the normal tissue complication probability, and those three lines are for if you have the entire liver radiated, two thirds of the liver irradiated or one third irradiated, and you can see there's a significant difference when you go from two thirds, to one third of the liver being irradiated, and there's a strong volume dependence in that region. There also appears to be a dose threshold where above 40 gray you see a significant increase in the incidence of radiation hepatitis. So again a summary of the literature on patients being irradiated for liver tumors. There are fewer series here, but the local control rates are high, with short median follow ups. There is some modest acute toxicity described in patients being treated to the liver, nausea, and

low grade fever are non-uncommon, but these patients can be prophylactically treated with analgesics and antipyretics, and this does not cause much morbidity for the patient. Blomgrens initial experience describe some toxicity, severe toxicity in patients, but if you look at that series these were quite large tumors that were treated and most people are not treating tumors this large to date. What are some other applications for body stereotactic radiation? Just touch on these briefly as Brian mentioned, spine metastases are often treated with a boost after the tolerance doses is delivered to the chord. Primary tumors and paraspinal locations have been treated by the group at UCLA and the adrenal gland there is one abstract from the Stanton Island group, showing that these patients can be safely treated, may have enhanced overall survival and finally the low alpha beta ratio that has recently been confirmed for prostate cancer, may lend itself to a

better control with hyper fractionated doses. So in conclusion what's possible with body stereotactic radiation, reduce toxicity of treatment appears to be feasible, alternative to conventional surgery or the other invasive treatments. Improved tumor control and hopefully this will result in improved patient survivals. Thank you.