

Thanks everybody for being here. As Dr. Indrin Chetty eluded earlier, Monte Carlo has a greatest impact in thoracic radiation, so my talk will discuss about lung cancer. The title is “Improving Results of Radiation Therapy in Lung Cancer: Impact of Dose Calculation Algorithm”... Let’s start with a case. This is a 69-year old male had a stage II non-small lung cancer with lung cancer with a tumor of about 139 cc. This patient was treated with high dose radiation per University of Michigan dose escalation protocol. The picture on the left shows a primary tumor of left upper lobe, located lateral to the great vessels. This patient received 103 Gy of radiation. Six months later he was found to have local recurrent disease, located posterior to the original primary. He had a local recurrence. This patient died in about 18 months.... Why did this patient fail? What are the potential reasons? Not enough dose? Bad tumor? Inadequate

margin? I don’t know? To answer this question, I think we have to go through some basics. We will first simply review the current status of lung cancer as well as pattern failure. Then will spend couple minutes on optimization of radiation therapy, focusing on updates of RTOG symposium, and specifically discuss about tissue heterogeneity corrections, and at end will share you long term result from University of Michigan dose escalation studies, discuss about the impact of heterogeneity correction. During the year of 2003 in the United States, a total of 170,000 new cases of lung cancer, 157,000 of them died. Non-small cell lung cancer which accounts about 80% cases with 5-year overall survival rate of only 10 to 15%, this is the focus of our discussion today. Treatment for non-small cell lung cancer is multi-modality. Surgical resection provides the best result. However, majority of them cannot receive surgery either due

to medical co-morbidities or due to extensiveness of the disease. Let’s look at the data from Surveillance Epidemiology and End Results of United States for years of 1995 to 2001. Only 70% of the patients with localized disease had surgery and only about 10% of them with local and advanced disease received surgery. What does radiation do? Radiation is the major local non-surgical treatment, is the only definite treatment for patients with medical inoperable early stage disease, those patients with localized disease, the local treatment for patient with unresectable disease (locally advanced disease) Radiation is also the local adjuvant therapy for high risk patient after surgical resection. The treatment result, however, from radiation based non-surgical treatment, not ideal. As you can see from the number here there are only about 10 to 34% of 5-year overall survival for localized disease. This is much inferior to that of surgery

which ranking about 50 to 70%. For patients with regional disease, the results are even poorer, less than 10% 5 year survival rate. Why? Is it because radiation is not effective? To answer this question, we need look into the pattern of failure. So how do they fail? For the patients with early stage disease after radiation therapy alone, about 50 to 80% of them failed locally. For the patient with advanced stage disease, after the chemo radiation therapy based on recently published **CALGB 8433**, about 50% of them fail local only, 50% of them have both local and distant failures. Roughly 90% of them have component of local failure. Local failure is a major problem, radiation may be responsible for the poor outcome. What is the problem? Does radiation work for lung cancer? Why it is so difficult? The major challenge of radiation, specifically lung radiation, is the limit of normal tissue toxicity. Here let’s look at the probability

of tumor control (TCP) and normal tissue complication (NTCP), the “famous” sigmoid shaped

curves. The X axis is the dose of radiation, and the Y axis is the probability. These two curves are very close to each other. Physicians are worried about toxicity so that radiation dose is not given higher enough for adequate tumor control. To improve the therapeutic gain, you have to move these two curves apart. From biologic standpoint, you can sensitize the tumor, to move the TCP curve to the left or desensitize normal tissue, using radiation protectant to move the NTCP curve to the right. Billions and millions of dollars have been spent, results from the last several decades are very suboptimal. I don't know of any radiation sensitizer being used in the practice except for chemotherapy agent. So what do you guys, medical physicists do here, is to target the tumor accurately to maximize, increase the dose to the tumor while minimize the radiation to normal tissue. Instead of moving these curves farther apart, you manipulate the relationship between dose radiation to the tumor and to the normal tissue. This is hypothetical.

The fundamental question is if dose really matters tumor control in our patients. Do we have evidence? The data from our patients is very lousy, due to multiple confounding factors. RTOG 7301 is the only randomized trial that demonstrated the dose response of local failure. It was a four-arm randomized trial, to examine the radiation dose effect. The 60 Gy had less local failure comparing to 50 and 40 Gy arms. RTOG 8311 also indicated a 69.6 Gy is better than lower doses. These are clinical failures. From standard point review of pathologic response, a study from Germany demonstrated that 60 Gy had 21% of complete response rate, while it increased to 64% with 80 Gy. This figure shows the data from patients with medically inoperable early stage diseases from several centers. These are the group of patients received radiation therapy alone as the treatment. As you can see here with increasing tumor dose, you

see a trend of improvement on local control. Well, considering that these are results from many different studies, this trend is quite encouraging, to radiation oncologists, and to radiation physicists. ...This slide shows the relationship between dose and toxicity. Dose also matters to radiation pneumonitis. This is again a compilation of five different studies showing the relationship between mean lung dose and radiation pneumonitis (grade 2 and above). With increasing mean lung dose, the incidence of pneumonitis increased. At 10 Gy level, increment of every Gy of mean lung dose would increase radiation pneumonitis by 1%, and the 30 Gy 2.5%. So, it is critical to minimizing mean lung dose by optimizing radiation therapy. In January of 2004, RTOG gathered the physicians, physicists, scientists to review and discuss about optimization specific topic . Dose response relationship in both tumor and normal tissue was

reviewed. A great emphasis was made on the tissue heterogeneity correction, specifically addressed on the dose calculation of heterogenetic correction. Features of the various commercial available algorithms from different vendors were also compared. In addition, they gathered chairs from the major cooperative groups discuss about their individual experience on heterogenetic correction. The first question they have if heterogeneity correction should be implemented in the clinical trial? Heterogenetic correction changes the dose at isocenter, the ICRU prescription dose. Correction factors for a 6 mv photon APPA beams in lung ranging from 1.05 to 1.13, varies with dose calculation algorithms. Heterogenetic correction also alters PTV coverage. Researchers at M. D. Anderson, did a study on 30 cases of early diseases when they first moved to heterogeneity dose calculation. Using pinnacle system, the three plans were

generated for each patient under same dose prescriptions: Plan one is a good traditional plan, the homo plan without implement heterogeneity correction. Plan two is same as plan one, same unit of beams weighting but with heterogeneity correction turned on. Plan three is a 3D plan, heterogeneity corrected, with dose prescribed to 95% of PTV to the same dose as plans one and two. They found that in 14 of 30 so-called good homo plans, had less than 95% of PTV coverage if heterogeneity correction was turned on. This figure shows examples of isodose distribution. The picture on the left is a so-called a good homo plan, actually had a quite large volume of CTV miss here on the tumor peripheral zone, at a region adjacent to lung. The picture on the right shows a heterogeneity corrected plan, with nice and adequate target coverage. The Netherlands group also studied a large number of lung plans that initially produced by EPL

(equivalent path length). Using same Monitor Unit, the doses of each plan were recalculated with convolution superposition algorithm. They found that EPL constantly overestimated the dose at tumor lung boundary at about 10%, over estimated dose of the lung by 17%, V_{eff} 12%. This picture shows a plan of very nice coverage with adequate margin under EPL calculation; very tight margins after the doses were recalculated by convolution algorithm. Without knowing the picture on the right, a physician like me, would accept this plan without any question. But if I would have known the true dose may be like this, I will not approve this plan. After about 20 years of hesitation and discussion, finally RTOG decided to move to heterogeneity correction. RTOG symposium concluded, the differences among various algorithms are much less compared to the difference between homo and heterogeneity correction. The heterogeneity corrected dose

calculation is the CORRECT way. During this AAPM, in the section of transiting to heterogeneity correction lead (by Eric Klein and Craig Steven), Eric summarized historic background on this topic, and presented TG-65 recommendations. Eric also commented that different kind of algorithms gave different results. Some of them largely overestimated dose. Dr. Steven summarized the experience from MD Anderson on heterogeneity correction in lung cancer and he commented for a couple times that physicians were “horrified” to see the differences between plans of heterogeneity corrected and uncorrected ones. As we discussed earlier, different algorithms give different results. How do we know which one is right? Why Monte Carlo? This figure will help to answer the question. For lung media, Monte Carlo calculated dose matched up the best with results of measurement. In patients, we found

significant difference on dose distributions from Monte Carlo versus EPL. Significant difference on the 95% isodose lines between MC and EPL under hetero setting. No notable difference was seen under homogeneity setting. EPL largely overestimated dose in the peripheral region of the tumor, in the boundary of the tumor and the lung, and as well as in the lung. At last, let's move to the clinic. We will review the long term results from University of Michigan studies. As mentioned earlier, we enrolled about 120 patients between 1992 to 2002. Patient was treated with 3D conformal radiation therapy targeting to GTV with .5 cm CTV margin, and 0.5cm+ PTV margin. No elective nodal radiation was given. The highest dose went to 102.9 Gy. EPL heterogeneity correction was implemented. Overall treatment result showed 5-year overall survival about 13%, and median survival 19 months. This number is slightly better than the best arm of RTOG 9410, concurrent chemo-radiation therapy. The predictors for survival were

analyzed. Significant unvariable predictors for overall survival under included GTV volume and total radiation dose. However, if you use multi-variable joint model, total dose become the only significant predictor for survival. Total dose is also significant predictors for both for progression free survival in both single model and multi-variable model. This slide shows an example of nice dose response in patients without distal failures. You can clearly see here as significant difference of overall survival for patient who received more than 75 Gy versus for the patient received less than 70 Gy. Here's an example of local regional progression free survival, a nicer dose response. For patients received highest dose (94-103 Gy) is much better than those patients received 63 Gy. But, please note, this is about 100 Gy, the recurrence is still quite high, about 40% (per Fletcher, this dose should have all the lung cancer controlled). Then we further looked into the pattern of failure and try to explore the reason. Patients had CT

images available at first recurrence were studied. We registered follow-up images with planning CT scan. The recurrent tumors were contoured blindly by a radiologist and radiation oncologist. Dose was also recalculated with Monte Carlo algorithm and compared to that of EPL. We have finished 14 cases of recurrence, and some of them failed in the center of the PTV, and some of them fail at margin. I will show you a few examples. This is an example of a marginal failure. This patient received a 75.6 Gy, the initial primary tumor was outlined in purple, there you can see a recurrent tumor. It is not difficult to tell this is a marginal failure. And this is an example of a central failure. This patient received 102.9 Gy. The plan was generated by EPL calculation, showing a nice coverage of gross tumor with adequate margin by 95% isodose line. I think I have no problem to approve this plan if I only look at the EPL isodose line (white). However,

with the Monte Carlo calculation algorithm, the tumor is barely covered by 95% isodose, with minimal margin for microscopic disease, organ motion and set-up errors. This tumor recurred, and the recurrent tumor was covered by 95% EPL isodose lines, but not the 95% isodose lines of Monte Carlo. In addition to the bad examples, I would also like to show you a good example. This patient is an example of success. We have a very perfect match of isodose distributions between EPL and Monte Carlo calculations. This patient had his tumor controlled, however, he did develop fibrosis and he is still alive at seven years after radiation therapy. Finally, let's come back to look at the case I showed you at the very beginning of this talk. With primary tumor next to the great vessels, we see sufficient coverage of target by 95% EPL. I would only concern a little bit of overdose here. With Monte Carlo calculation, this region became quite tight on

coverage. This patient developed a recurrence; the possibility of underdosing due to tight margin couldn't be ruled out. Looking at the group of patients we have so far calculated by both Monte Carlo and EPL, the equivalent uniform dose to original GTV differs about an average of 2.2 Gy (95% of interval from 1 to 3 Gy). This is statistically significant. The equivalent uniform dose for original PTV also differs significantly. Mean lung dose differs by 1.4 Gy. Consequently the NTCP estimation would also be significantly different. EPL overestimates the doses... What's the potential consequence of miscalculated dose? Let's do a simple calculation. If you believe there is dose response in tumor control, if the tumor is underdosed by 2 Gy it would cause local failure in about 1 to 2% of patients. This may translate to 1500 of Americans every year. If the mean lung dose is over estimated by 1.4 Gy, which means because concerning of normal tissue

complications you would decrease your tumor dose by 4 Gy. This may translate to another 3000 Americans every year. Most importantly, over estimation of the dose at tumor and lung boundary may cause marginal failure. One failure in ten patients, that's 10%. How many patients? In conclusion, Monte Carlo provides more accurate dose calculation to tumor, to normal lung, and most importantly to tumor lung boundary. Every Gy counts. Every failure matters, to the patient, to patient's family, and to the physician. At last, I would like to express my sincere appreciation to the great team from the University of Michigan. This is a result from team efforts for duration of over ten years. Listed are only parts of the great team members. Thank you !