

>> Recording started.

[Background Sounds]

>> I'd like to thank my speakers again, the speakers today for participating on this panel discussion. And once again we have Dr. Howell. Dr. Rajaraman. Dr. van Leeuwen. And Dr. Lipshultz. So today's panel discussion is going to be on medical radiation and dosimetry. Any discussion topics from this morning and this afternoon are fair game.

[Background Sounds]

This is an interactive question and answer session.

>> This is a question actually I already discussed with Dr. Lipshultz. And he thought it was interesting, so I'm following up with the panel. It's actually following up on what you were saying, Preetha, about survivorship programs. I'm suggesting that mobile apps, putting these surveys online and actually recruiting people. At least, as Steve said, you know, they sort of, they're the survivors, they don't want to think about it. But they're also the survivors who are focused on it. And you might be able to get some interesting information that way so.

>> Well, what I was saying to you before is I think that that is really important. It is not happening in any uniform way right now. Why do I think it is so important? At least in United States for childhood cancer survivorship, everybody who hangs out a shingle in this field claims that they have comprehensive programs. They spend a lot of time, and they do everything. At least when we've gone out and abstracted records of programs and feed it in, the visits are usually quite short. And they're really more medically focused. And really having the time in advance to really go through standardized instruments to identify areas where there might be a need to look a little bit further. Because, if you look at the Children's Oncology Group survivorship guidelines for monitoring. If you really employed every single one of them, the patient would be in for about a month. And the cost would be enormous. And you get enough data that's positive that you wouldn't really quite know what to do with it. And, if you don't follow it, you're not necessarily a good doctor if somebody has an event. So I think here, if patients can fill out certain standardized forms, at least looking toward conventional risk, it at least helps you focus in on what might be areas of concern. Because, as I showed, you just ask a generalized question in a 12-minute visit, how are you feeling? You may get information that may be a little bit colored by their prior experiences.

>> In the Netherlands there's already an app being used for testicular cancer survivors. That has their survivorship care plans. And maybe questionnaires could be added to that. I'm sure that those investigators are thinking about that. And for the survivorship program that they are developing for survivors of adult Hodgkin lymphoma, we are also considering something like that. So I really think that's a very good development.

>> I mean, in the Netherlands over the course of the last year or so, there's been an incredible effort to nationalize the entire nation in this regard. And I think it's a model system in many ways.

>> True.

>> I have a question for the panel. There's been a lot of talk about external radiation and very little about internal radiation. And in the research world, particularly in radio chemistry we're interested in targeted alpha therapy. And I was wondering how, just what the thoughts are, the panel, on the cancer risks associated with large doses of alpha therapy? And also how you might approach dosimetry associated with that?

[Background Sounds]

>> I can comment on dosimetry side only. So you're talking about the nuclear medicine where is completely different from external radiation dosimetry. So on the same side with NCI something series, because I've been working on the NCINM, which is nuclear medicine side. So this is, conventionally they're based on the conventional stylized phantom-based dosimetry. But now we are moving to more realistic anatomy-based computation of phantoms. So using that phantom you can more calculate the accurate, more accurate radiation dose from targeted radiation therapy, targeted alpha-particle therapy or other types of procedure thing. And then at the same time, when you go into the patient anatomy, so more and more you're going to see much more high degree of individual availability. So in that sense, you cannot, you may not want to utilize this phantom-based calculation. So like I said in my talk, more individualized CT dosimetry. [Inaudible] that you need to more individualize your calculation. Because you're, talked about the patient-specific dosimetry not population-based or phantom-based dosimetry. So, you know, I've been exploring other option to, two options. One is that automatic segmentation that I showed you in my CT talk. And at the same time, can we morph our pre-segmented phantom to match patient anatomy, to get more patient-specific dosimetry. So we are on that track right now on dosimetry side. You can comment on that.

>> So for retrospective dosimetry, as Choonsik was saying, that would be very challenging. I think the one thing to consider about alpha and some of the other treatments, the outer-field dose itself, the physical dose is going to be lower because there's such a rapid fall off with the alpha particles and how far they travel. Their relative biological effectiveness is higher, so it's going to be more concentrated in the areas that are nearby. Which is information that you would have at the time of treatment. So this is the kind of information that really needs to be collected at the time of treatment. Because it really, probably reconstructing it would be nearly impossible for an individual patient. But the out-of-field dose, as you get really far, to far away organs, would be much, much smaller than from external being just like with brachytherapy.

>> So not commenting on the dosimetry, of course. We have our two experts. But one of the points that I'd made about the radiation signatures that we're looking for is certainly the two that were

identified most easily were ones where we knew a lot the about the kind of damage that there was. So this is actually a question that I'd really like to throw out to the radiation biologists and chemists out there in terms of, are there particular settings or particular kinds of radiation exposure in which you would think there would be particularly unique kinds of damage? And would really welcome thoughts from the audience on that.

[Background Sounds]

>> So I have a question a little bit going back to what Mark was asking. How to understand this effect of relative low doses. So is there research going on in this field of diseases which really directly focus on stem cells? Because, if he's talking about thin wall, it might be basically that the number of cells which can produce new cells is really severely reduce even by low doses of radiation. So the question, is there any research going on in that direction?

>> Well progenitor cells and stem cells and the heart are a small but real population, okay. In the developing heart, historically, people have felt that by six months of age a 60-gram left ventricle has all the heart muscle cells needed to form a 300-gram left ventricle in an 18-year-old, an adult-sized ventricle. And it's with minimal hyperplasia and almost exclusively by hypertrophy of existing myocytes. Over time there's been a realization that within the heart, that the population of binucleated cardiomyocytes increases over the first two or three decades of life. Suggesting that they're not terminally differentiated, you know, mitotically quiescent. On the other hand, that is not necessarily from a robust progenitor cell population. Again, a perfect example is after a myocardial infarct you're left with an infarct. You're not getting replacement. You're getting fibrosis. So in a normal healthy situation, it's still a very, compared to other organs, it's very limited. In the setting of cancer, the most sensitized population, at least in terms of anthracycline, not as well studied for radiation. For really damaging in a significant way are the stem cell progenitor populations within the heart. So they're limited to begin with, but they're preferentially damaged or destroyed with at least anthracycline chemotherapy. More so than with the terminally differentiated cardiomyocyte. Now, the real question is, is so what does all of that mean when 70 percent of the cells of the heart are nonmuscle cells? And what is the effect on all of the other populations as well? Because, when I talked before about having a restrictive cardiomyopathy with less compliance and less relaxation, that speaks in some ways more about the matrix and the, you know, and the other populations of cells in the heart. Now, we know that with anthracycline it disturbs wound healing and you wind up actually getting less fibroblast proliferation. Less extracellular cardiac, you know, matrix developing. With radiation, it depends on the model and the circumstances to how much of an effect you have. But getting back to your question, you know, in preclinical models there's been some work looking at progenitor cell populations in the heart with regeneration. Whether it promotes in essence whether it has other effects. But it's, even under a healthy heart situation, there's not enough stem cells or progenitor cells within the heart to deal with the reparative process in cases where

it's more than a couple of million out of a couple of billion dead or damaged cells.

>> Thank you.

[Background Sounds]

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>> I had a question going back to the diagnostic imaging part of the morning. Obviously, we're talking about CT scans. And there's a lot of work being done to reduce the dose. But what about alternative modalities? You know, what role do PET scans or MRIs have in this?

[Background Sounds]

>> Well, you know, I think that in the clinical arena we're increasingly utilizing more MRIs. In part, at least in the states, the reimbursement have become more uniform in that regard as well as the availability. In children's hospitals we now have some children's hospitals with as many as six or seven MR machines. And, if you don't use them, that's a problem. So we're using those more. I think that, increasingly, functional imaging becomes an issue. And we're seeing an increasing number of centers doing PET specifically to get more functional data with a variety of different tracers. And, even though those are short-lived in terms of risk, it does raise questions. Especially in a number of the patients that get those. They get them serially in a repeated fashion. Not just for assessment of recurrent oncologic disease, but from perspective cardiac or other organ functions. And we anticipate that that use will actually increase, not decrease, over the next five or ten years.

>> In Hodgkin lymphoma trials in Europe, PET scanning issues increasingly for follow-up. Because the initial treatment has actually really reduced radiation doses and volumes and also lower doses of chemotherapy. So in the follow-up of these patients, yearly PET scans are getting very normal. And that really causes increasing doses of radiation. And actually Michael [inaudible] and I have an idea in the Netherlands to do something with that inside of a study. In a very preliminary stages, yes.

>> You know, from a clinician's perspective, you know, it varies. There's some that say there's too many false positives. But, on the other hand, if you can pick up on recurrent disease at a half sonometer as opposed to two. You know, from a patient's perspective, that's desirable.

>> I think one thing also to keep in mind, a lot of PET is done in conjunction with CT. So that the anatomy can be registered and fused. And so it's just increasing the overall burden. And then with respect to MRI, it depends on what part of the anatomy you're imaging. And it's very patient specific. So, if you need soft tissue differentiation, then MRI's the ideal choice. But often times you really do need certain things with respect to a CT. And in, particularly, in radiation therapy, we need CT scans for our dose calculations and things that MR just can't do. So,

even if we have a CT scan or, I'm sorry, an MR scan for image differentiation, we still need a CT data set as our primary.

>> So the whole issue that, you know, you almost always, to localize or doing PET these days in the setting of PET/CT, we also see that, you know, increasingly we're using more and more PET/CT in younger and younger ages. So like, for example, as we see that this has increasing prognostic value, let's say in an asphyxiated newborn looking at brain function. Or somebody with seizures and looking at [inaudible] for seizure activity and the like. We see in young children that might have an increased radiosensitivity probably an increasing use. Because the validation that these have predictive value and meaning between not only function then, but subsequent neurodevelopment, neuropsychologic, that it's, they're falling more into play. And I would anticipate that over the next five years or so that may be an area where there will be. It would be very nice to understand what the effects of that really may be.

>> I have one final remark before I have to leave to catch my flight. I think there are a lot of initiatives such as image gently and image lightly which have recommendations to minimize dose for individual patients and scan sequences. And it is a big movement within the medical physics community to use the appropriate protocols so that every scan has the least amount of dose possible. And the implementation of those protocols is really quite widespread now. And now I have to dash.

>> Yeah. And following up on that actually. If any of you recall Amy Berrington's slide this morning, where you actually saw the numbers of CTs going up and then starting to come down in 2011. I don't think that was any coincidence. I do think that the work that we as radiation scientists do here at REB and elsewhere does actually make a real impact.

[Background Sounds]

>> I have a question for the panel. So I was talking with a DOE colleague here. And he was impressed with the dosimetry and the quality of the studies for medical radiation. And, of course, now the atomic bomb survivors is a gold standard for radiation and health outcomes. Can the research from epidemiologist studies from medical radiation, could they ever get to a stage where they are a copper or a silver standard. Or get to the really quality outcomes such that they could be the new standard for determining exposure and outcome. And sort of additional an question is, what additional resources for the types of research that you're doing, what would bring your research to the next level?

>> Well, that's a challenging question. I think that the atomic bomb survivor data are particularly important for the low-dose range. And that the medical radiation data, and now I'm just ignoring for a minute the CT data. That the medical radiation data are very important for the high-dose range. And those [inaudible] really need each other. It's even possible that the dose response in the very-low dose range for some disorders like the heart may be slightly different. We still don't know that. So it's both very important. And I would actually say that there are a lot of medical radiation studies in the high-dose range, where I would say that the quality of the data has been extremely high. For

physicists this is certainly true that there's been enormous efforts to get at all these radiation charts. It has been very expensive. But also there are a large number of European studies that have also worked actually with Marilyn Stovall, where the quality of the radiation charts has been extremely good. For example, in the Netherlands we've been very fortunate that most of the radiation centers have kept their records for very long periods. And, if you get access to the radiation charts and the simulation films, then you have very hard data. And I would challenge the audience by saying that maybe the dosimetry would be even better than for the atomic bomb survivor data. Because, of course, we all know that they're, we've had lots of discussions about the right doses. And the doses have been changed over time and all that.

>> So I would completely agree with that in terms of, many of the radiotherapy studies that have been done are extremely high quality data. And the outcomes that have been assessed there are quite accepted actually. I think where there is more uncertainty really is in the low doses of medical radiation. And that's the gray area.

>> Diagnostic.

>> Yeah.

>> So I want to comment on the dosimetry [inaudible]. And, yeah, in my talk I mention that the medical radiation is much controlled. And then we don't have that many unknowns compared to environmental, let's say, atomic bomb survivor. And another thing is, more and more we are moving toward, I remember one of the audience asked a question about electronic file for everything compared to those paperwork. So more and more we are moving toward more electronically comprehensive data whenever patient get diagnostic radiation and therapeutic radiation. So one of the effort, instead of, we've been working largely on the retrospective, dose reconstruction is huge effort done by Marilyn Stovall so far. And then another aspect is kind of more medical radiation reconstruction moving toward electronic file base, DICOM files and all of those other resources available. So I expect that the radiation dosimetry itself for more recent and modern database will be much more high quality compared to retrospective dose reconstruction part. So part of the collaboration so far, nowadays we are working on the proton therapy clinical trial. Or, CT itself is, for example, APCT study, European effort, they're working on the DICOM file itself instead of paper-based survey or other things. So, when you actually get that DICOM file, you're going to do much higher level of accuracy in dosimetry. So, you know, using, based on those effort and based on real electronic file base dosimetry, so dosimetry quality itself is much higher than other database. So, you know, in the near future, near term future, that data set collected and collected. And at some point it will be very high standard resource for future epi study I think.

>> Just a comment following on from that. I mean, well, first of all there have been a number of validation studies, haven't there, comparing, well, validating various types of medical dosimetry against each other and also against various biological measures. And in general they confirm what you said. I mean, I guess the uncertainty in relation to radiation

therapy is often knowing where the target tissue is. You know, where the target cell is in relation to cancer. And though, you know, although doses may be very accurate as in a tissue, you don't know precisely which part of the tissue to look at.

[Background Sounds]

>> I am very new to this field. But I thought I'd just ask this question. That I've heard a lot about genomics and genes, but not so much from a metabolomic point of view, which is closer to phenotype. Why not go there? Especially for a low-dose and low-dose rates, where you don't particularly get cancer? But you do get signatures that may define better what you're looking at? So just a comment. But maybe proteomics, metabolomics or lipidomics would be closer to phenotype than genomics. Especially in a human population with so much variability there.

>> So I think that's an excellent point. Two part response to that. The first is, in some sense this field has been driven a little bit by where the technology has been the best. And certainly the technology in genomics has moved much faster. And in terms of getting down to an expense where we can do it in populations then the other fields. So that's part of it. The second is also thinking in terms of outcomes. So certainly a lot of what we have focused on in the National Cancer Institute certainly has been cancer outcomes. And so, when you're thinking about the proteomics, metabolomics, et cetera, I think you're absolutely right that those would be fascinating to study in the shorter term outcomes. And, but there may well be studies ongoing. And, finally, I think, as these techniques are getting better, the idea is very much to integrate what we've learned from the genomics with new data. Hopefully coming in from metabolomics and proteomics. So, yes, we're going there.

>> Probably have time for one more question before our next speaker [inaudible].

>> Well, thanks. I may have a question more about genetics as well than about radiation. And so, yeah, but one way of doing GWAS, the way, like mainly we worry about population stratification in case that the population involves some heterogeneity. But I'm sure, like in open-ended studies, heterogeneity must be an unwelcome choice. But still I'm curious about how the, like what the population condition is for these studies? Thanks.

>> So for those of you who don't know what population stratification is, it's a fancy term for saying confounding by ethnicity. And even though I think geneticists initially thought this was going to be a very, very big problem in genetic studies, it's actually turned out to be less of a concern than you would really worry about. So unless you're doing something really unreasonable, like having all of your cases come from the U.S. and all of your controls come from Japan. In general, we found that, even without the control flood stratification, you find your signals. But certainly where you do need to do it, it's fairly straightforward to do that with the ancestry markers.

>> Let's give our panel discussion a hand. Thank you.

[Applause]

And I'd like to invite Dr. Hatch back, course coordinator, to introduce the next speakers.