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**Health Technology Clinical Committee Public Meeting**  
May 17, 2019

Gregory Brown: Good morning. I'm Greg Brown. I'm the chair of the Health Technology Clinical Committee, and we are a few minutes after 8:00. I'm going to start our session today. I'd like to welcome you all. We are going to start with some updates and then previous business meeting for our January meeting minutes. I had recused myself as chair on that topic. So, Dr. Rege is going to share that part of the meeting. Then, once we're done with the January minutes, then, we'll get into our proton beam therapy review. So, we'll go from there. So, first, any updates?

Josh Morse: We do have our, or do we, have our slide presentation for starters or? So, we have a few slides where we just do a brief background of the program and some meeting . . . just some reminders about the meeting itself. Let's see if I can find that presentation myself on my computer here. OK. Well, I think I can do this without the pictures. This is just a few slides. So, my name is Josh Morse. I'm the program director for the Health Technology Assessment program. Today's agenda, on the agenda, there is the past meeting business from the January meeting, which includes two subjects, the peripheral nerve ablation topic and the sacroiliac joint fusion. So, some meeting reminders. This meeting is recorded. A transcript of the meeting will be made available after the meeting. It takes a few weeks for that to occur. It's then available on our Health Technology Assessment website at the Health Care Authority's website. So, just a reminder, when participating in any discussions, we ask that you please state your name and also please use a microphone. And if we need to, we'll try and remind you. That helps our transcriptionist keep an accurate record of what's going on here. Finally, to provide any public comment today, if you have not already signed up, we do have a couple clipboards out there. You can put your name down on the clipboard. Please note on there if you plan to speak if you haven't already done so.

So, a bit about the Health Technology Assessment program. The Health Technology Assessment program is managed by the Health Care Authority,

the Washington State Health Care Authority, a State agency located in Olympia. This program and process were created through legislation, and it's designed to use evidence reports, and this panel of community clinicians, to make coverage determinations for selected medical procedures and tests based on the evidence for their safety, efficacy, and cost-effectiveness. So, agencies that participate in this program include the Health Care Authority and its Uniform Medical Plan program, and the State's Medicaid program, which is also known as Apple Health. Also participating are the Department of Labor and Industries, and the Department of Corrections.

So, the purpose of the Health Technology Assessment program and this process is to ensure that medical treatments, devices, and services paid for with State healthcare dollars are safe and proven to work. The program provides resources for the state agencies that purchase healthcare. We use this process to develop scientific evidence based reports on the selected medical devices, procedures, and tests. Then, our program staff from the Health Care Authority facilitate this committee's work who ultimately determine what the coverage determination should be for the medical devices, procedures, and tests that have been selected.

This is a high-level view of the process. If you could go back a slide, Christine. Thank you. So, topics can be nominated by anybody, including the State agency medical directors. The nomination and topic selection process goes through a public review process where there is the opportunity to comment on topics that are proposed and ultimately selected. The director of the Health Care Authority has the authority to select technologies for this process. We then develop a key question or research plan for the technology assessment. We have independent contractors that write these reports for us. These also go through a draft public review period. Ultimately, the report is brought to this group in public meeting, as we are today where the committee contemplates the information, hears from public comments, and then makes a draft determination. Following the draft determination, as the past meeting business agenda item today, once the committee makes any final determinations on those, the agencies are charged with implementing the coverage determinations from this group.

So, further on our calendar for this year, today is May 17<sup>th</sup>. Again, this is the proton beam therapy. We'll be doing a rereview after the previous meeting business. Then, on July 11<sup>th</sup>, we have a scheduled phone conference, or a webinar, to revisit any draft decision from today on the proton therapy question. The committee will meet July 11<sup>th</sup>. September is typically a time reserved for the committee's retreat. Then, in

November, we currently have scheduled two topics, a review of whole exome sequencing, and a rereview of femoroacetabular impingement syndrome.

So, how to participate with our program, as I mentioned previously, we have a website on the Health Care Authority homepage. You can find our Health Technology Assessment program. Anyone may sign up to receive Health Technology Assessment program notifications via email, also available at that website, which is on this slide. Anyone may provide comment on proposed topics, key questions, draft, and final reports, the draft decisions, and also at the meetings, as we are today. Anyone is welcome to attend these public meetings and present comments to the committee or nominate health technologies for review, and that is my summary. Thank you, very much.

Gregory Brown: OK. Thank you, Josh. We will then move into the next part, the January meeting minutes, and I will turn it over to Dr. Rege.

Sheila Rege: Hi, my name is Sheila Rege, vice chair of this committee. If we can all go back to the minutes, which is on the first page of our binder and review them for accuracy and let me know if there are any questions, or I'll entertain a motion to accept.

Mika Sinanan: Motion to accept.

John Bramhall: Second.

Sheila Rege: That was John for the record. Any discussion? OK. Everybody in favor?

Group: Aye.

Sheila Rege: Perfect.

Josh Morse: All approved?

Sheila Rege: All approved? If we can go on, now, to . . . we have received several emails and letters that are in your binder. I would like to open that up for discussion, because our next step will be reviewing these and based . . . And kind of going to a vote prior to final adoption. The key questions we're going to have are based on public comment, was evidence overlooked in the process that should have been considered? Or does the proposed finding and decision document clearly and convey the intended coverage determination? So, I would like to open it up for discussion before we go to those questions. To help along, Dr. . . .so there is a lot of organizations

that commented, including some who presented at the last meeting, the American Association of Orthopedic Surgeons, the . . . Dr. Polly from University of Minnesota. The International Society for Advancement of Spine surgery has included coverage criteria for 2015 and 2016. The Neurologic Surgeons, the American Association, the Congress, and the Washington chapter have written a letter. So, in January and February, Spine Interventional Society. Then, on April 9<sup>th</sup>, there was a question that I think we need to give guidance on asking about our statement about coverage, due to osteoarthritis or other conditions, whether we wanted to parse out what other conditions or just leave it as other conditions. There is a March 2019 published paper that is out here, included in your packet, too. Reading it, Halyard Health it sounds like sponsored this. This is the paper that may have come out after our meeting. I will open it up again for discussion. Let's do a straw poll.

- Josh Morse: So, I think, just to clarify, are you doing the SI joint fusion decision or . . .
- Sheila Rege: I'm sorry. I'm doing the SI joint fusion.
- Josh Morse: Or the peripheral nerve?
- Sheila Rege: No. I was doing the SI joint. And I'm sorry. I mixed those two together. So, would you like me to take them separately?
- Josh Morse: Well, the question about the osteoarthritis, I think, was for the second one, peripheral nerve.
- Sheila Rege: So, let's do the SI joint one first.
- Josh Morse: Thank you. Any questions? Any . . . on a straw poll, leaning towards where people are thinking. Are people thinking that evidence was overlooked? Anybody who feels that way kind of just do a hand raise just for . . . OK? In that case, and this is, again, for the SI joint, let's . . . I'll entertain a motion and we'll vote on it.
- Mika Sinanan: Motion would be that we retain the coverage decision, as previously stated, that the comments are insufficient to either reopen or change the coverage decision.
- Sheila Rege: Correct. Kevin, you look like you were getting your . . .
- Kevin Walsh: Well, I'd just like to comment, we're kind of at the mercy of the literature review. I feel that the process is set up to try to be comprehensive, in terms of addressing the question, and the technology. I think the State

does due diligence to try to find competent agencies to provide these reviews. So, to be second-guessed after the fact really is kind of addressing the process to me. I think that we try to be consistent, and we have a process for rereview when new literature is published. So, this . . . is the study that you were referring to, the March study, is that for the different, is that for peripheral nerve?

Sheila Rege: No. Actually, that was osteoarthritic knee pain, the study I was referring to.

Josh Morse: That's for the second topic.

Sheila Rege: The second topic, not the first one.

Josh Morse: That's the second one.

Sheila Rege: So, we're doing SI joint right now.

Kevin Walsh: So, my comment probably would address it, as well, in the sense that there is always gonna be new literature, and if an agency has the capacity to review that study deems it significant, it's going to come to the State, and we will be asked to rereview it. So, I don't think this is a closed process, but in terms of what we were given, I don't find that it's necessary to go back and re-question the decision.

Sheila Rege: So, we have a motion, and it sounds like, for the SI joint, everybody is comfortable. So, we can go to kind of the, the final vote. Mika, I'm going to take the privilege of taking a final vote about whether we approve the findings and decision document as is for the SI joint. Everybody in favor of that? Aye? So, we've got how many yeses? Seth? And Greg is? SI Joint. OK.

Josh Morse: We should check the phone. We may have Dr. Friedly and/or Dr. McMillin on the line, as well.

Janna Friedly: Hello? This is Dr. Friedly.

Sheila Rege: We are looking for a vote from Dr. Friedly. If you would . . . if you were listening in, we were voting on, does the committee approve the findings and decisions, as is?

Janna Friedly: Yes. I agree.

- Sheila Rege: Moving on to the limb pain, the RFA, the osteoarthritis. We'll go through the same motion, and I think Kevin has already spoken to that. Do we think, based on the public comment, was any evidence overlooked? Do we want a discussion on that? This is where the question came up if we wanted to enumerate, because we said due to arthritis or other conditions, whether we wanted to give anymore clarity. We left it as is. So, I'm opening it up for discussion. We have 60 seconds. I'm artificially making that up. It doesn't sound like anybody is going to be taking that. OK. In that case, then, just a straw poll. Is everybody ready to vote? OK. So, now does the committee approve the findings and decisions that we had enumerated at the last meeting, and I will take a vote.
- Josh Morse: Eight present in favor and . . .
- Sheila Rege: Let's ask Dr. Friedly . . .
- Josh Morse: . . . Dr. Friedly?
- Sheila Rege: . . . also. Is she on mute?
- Janna Friedly: I'm in favor of our previous decision.
- John Bramhall: Sheila, I just want to echo what Kevin said, to be honest, about both of these studies. We looked, in particular, the SI joint study that we looked at. I think it was a particularly good example of a literature review by the vendor. At least, that's my recollection, that it was a good presentation and if not exhaustive, certainly a representative review of the literature that we looked at, at the time. We had a particularly cogent guide with us, Dr. Kleweno, for that particular case, who took us through it a little bit more subjectively. So, I think it is the case that there is always going to be either new information that appears since our decision, fine, or a particularly pointed request for rereview and reinterpretation of papers that we have looked at dispassionately by people who have got a particular excitement and interest about the topic. I don't think it's necessarily wise for us to sort of spin the ball again, because of a couple of letters to be honest. I think the logical thing is to rereview when the body of information has increased substantially. I think we're always happy to do that. We review the topics. That's what we're doing.
- Josh Morse: Right, and because there are questions about this, we did add to this. These two questions from your decision aid about, based on the public comment, was evidence overlooked in the process that should be considered. That's really a safety valve question to make sure that if we made a mistake in our process with the vendor, if there was a paper that

they should have included, and it wasn't, and somebody points that out, we want to be able to go back and make sure we didn't miss that. So, that's what that question is about. We've added these questions back into the . . . this part of your binder, just for process.

Sheila Rege: But no, Kevin and John, I would agree. I think we . . . our contractors do a really good job of getting us a good review, and this is just a second check. Is there something that was missed? Not new data. If there is something, I mean, I'm a cancer doctor. If something miraculous that cures cancer, of course, you're gonna go back and redo that, but that's different. Well, that concludes that particular section. So, I will turn it back to Dr. Brown.

Gregory Brown: Thank you, Dr. Rege. So, we will start proton beam therapy rereview. I staved introductions for this, so that we could do two things. One is introduce ourselves on the committee. Second of all, if you feel that you have any perceived or potential conflicts, if you could identify them. So, I am Greg Brown. I'm an orthopedic surgeon with Franciscan Health in St. Francis in Federal Way. I do not have any conflicts.

Sheila Rege: I am Sheila Rege. As a radiation oncologist, I am president of the College of Radiation Oncology where we have, at our annual meeting, accepted money from companies that make proton devices. Josh and some of the agency people also asked us to look at our conflict statements closely. I called a financial advisor who said, oh, yeah. We hold some stock in a company that makes proton machines. He was not aware it made proton machines. He doesn't know what we talk about. So, with that, I talked to Dr. Brown and I am happy to participate in the discussion if the committee allows me to. I would like to recuse myself from the vote, just because of optics.

Gregory Brown: John, we'll start at your end.

John Bramhall: I'm John Bramhall. I'm an anesthesiologist specializing in trauma treatment. I work at Harborview Medical Center, and I know of no competing issues for me.

Laurie Mischley: My name is Laurie Mischley. I am a naturopathic physician in a neuro-epidemiologist, and I have no conflicts of interest.

Tony Yen: I'm Tony Yen. I'm a hospitalist and have no conflicts of interest.

Kevin Walsh: Kevin Walsh, family medicine. No one pays family medicine to do anything. So, I have no . . .

- Group: [laughs]
- Chris Hearne: I'm Chris Hearne. I'm a nurse practitioner, and I have no conflicts of interest.
- Seth Schwartz: I'm Seth Schwartz. I'm an otolaryngologist at Virginia Mason specializing in otology, and I have no conflicts.
- Mika Sinanan: Mika Sinanan. I'm a general surgeon working at the University, and I have no conflicts.
- Gregory Brown: And then I'm going to let . . . since we have a Dr. A, as apparently unpronounceable. So, I'm not going to try, and our expert for this topic.
- Smith Apisarnthanarax: I'm Smith Apisarnthanarax. I'm a [inaudible] at University of Washington. I'm a radiation oncologist. I primarily treat GI cancers and prostate cancer. I do use both protons and conventional x-ray radiation in my practice.
- Gregory Brown: Thank you for joining us today. OK. I think then we are ready to start with the State's presentation.
- Judy Zerzan: Good morning, everyone. This is my first time presenting in front of you. It is very exciting, and I thought, I will wait for them to have my special slides. So, let's move on into proton beam therapy. This is a review of the previous time that the committee reviewed this topic. It was adopted in July of 2014. The coverage decision was that proton beam therapy is a covered benefit with conditions. The limitations include that it is covered for ocular cancers, pediatric cancers, central nervous system tumors, and other nonmetastatic cancers with the following conditions: The patient has had prior radiation in the expected treatment field with contraindication to all other forms of therapy and at agency discretion. I want to point out to you that we have really moved away from the, at agency discretion. It's sort of hard to figure out exactly what that means and where.
- So, this rereview is . . . the basis of the rereview is that there is a fair bit of newly published evidence. This review covered both adult and pediatrics, as the first review did, and there were 189 new studies that met inclusion criteria, and the quality of the studies was marginally better than the last time that the committee looked at this topic. Table A in the evidence summary really provides that sort of overview of where the evidence falls. In general, almost all of the new studies, even though they are marginally

better than the last time, they are still of low quality or very low quality. So, we'll go over the results of that.

I think everyone here presenting is going to do a quick review of radiation therapy, and radiation therapy has really advanced a long way, um, and particularly, I think, in the last ten-ish years. The goal of radiation therapy is to damage cancer cells while minimizing damage to the healthy cells. It used to be all of two dimensions. No, everything is three dimensions and sort of standard. Radiation therapy is a 3DRT that delivers radiation to a 3D volume using imaging studies and software to precisely target delivery. Intensity modulated radiation treatment is a further development of this 3DRT using the same imaging findings, but it alters the intensity of the beam to sort of spare organs around and allow for more control. Then proton beam therapy, which we'll be talking about today uses a beam of protons to radiate disease space.

Proton beam therapy is largely a theoretical context, in terms of how it is different from these other conventional therapies. Protons are negatively charged parts of atoms, if you harken back to your high school or college chemistry or physics classes. So, they contain an exit dose. So, tissue past sort of the target of the radiation also gets radiation to it. That's sort of the main part at the target. Protons are heavy positive charged particles. So, they deliver most of their radiation at the point where they're aimed, and the normal tissues beyond this target receive little or no radiation. So, you can sort of see the region where it is . . . the white part is proton beam. The red is sort of the traditional x-ray, proton beam radiation.

So, the key questions we looked at, there are five. First is comparative impact of proton beam therapy with curative intent. The second question is salvage treatment on survival, disease progression, health related quality of life, and other outcome.

Key question three, what are the comparative harms associated with the use of proton beam therapy relative to is major alternative, looking at both acute and longterm toxicities, looking at systemic affects, toxicities specific to each cancer type, and risks of secondary malignancy or changes in radiation dose.

Then, the last two questions, is there differential effectiveness in safety of proton beam therapy according to a variety of factors listed here. Five, what is the comparative cost-effectiveness of proton beam therapy in the short and longterm. You'll hear later by our contractor, the cost-effectiveness studies found were really quite flawed. So, I'm not addressing this question in my overview.

This is why the agency medical directors decided to rereview this topic. We have medium safety concerns and high on efficacy and cost.

I'm going to start with doing an overview of what our utilization has been, both on the public employee side, public employees Medicare, and on the Medicaid side. So, these were the diagnoses codes we looked at, which is pretty much every kind of cancer. Then, these are the procedure codes that we looked at. So, this first table is looking at public employees on the top in UMP, Uniform Medical Plan. The bottom box is Medicare on UMP. I'll note, and it says here, but just to really drill home, for Medicare we're the secondary payer. So, the reimbursement amounts are quite low. Overall, you'll see from 2013 to 2017 the total number of patients that got proton beam therapy is 63. Most of these were on the Medicare UMP side. Sessions for proton beam therapy and, again, I would say any type of radiation therapy vary by the number and by the cost by site. Every category when we broke down, I'm not breaking down the types of cancer that we have treated, because the numbers are really quite small. In every category, there are a couple of people that go one or two treatments and then stop. We're not quite sure why. This is all claims therapy, but you can see the other piece that I want to call your attention to is that the average paid per session has dropped. This is similar to what has happened across the country in the cost of this type of therapy.

So, moving onto the Medicaid population, and this includes both our managed care and our fee for service population, over the same period of 2013 to 2017, 183 people on Medicaid were treated with proton beam. You can see the average number of sessions and average paid per session. Again, there is a fair bit of variability here, as Medicaid does not reimburse the same as other payers, that amount is lower.

So, in the original decision, there were differences between adults and pediatrics. So, we wanted to call out the differences. So, this is a total number of people on everything. So, PEBB, Medicare, and Medicaid each year, and the percent of those in blue are kids. Then, the red is adults. So, roughly 20% of kids . . . or roughly 20% of people who are treated with proton beam therapy are kids. So, you can see about where that fits in the pediatric cancer.

Our current state agency policies follows the committee's decision, and I will briefly go over some other payers' coverage policies. Each of these coverage policies, you will see when it was last reviewed, and most of them have been reviewed in the last year or two. So, Aetna covers proton beam therapy for chordomas or chondrosarcomas, for malignancies in children,

and uveal melanomas confined to the globe. United Healthcare covers it for intracranial arteriovenous malformations, ocular tumors, skull-based tumors, localized unresectable hepatocellular carcinoma with conditions, and it may be covered for a diagnosis that isn't listed in selected cases.

Cigna covers chordomas and chondrosarcomas at the base of the skull, uveal melanoma when it's considered preferential compared to brachytherapy, selected cases of localized unresectable hepatocellular carcinoma, seminoma, and malignancies in children. Medicare, the last time this was reviewed had a National Coverage Decision they have since retired that coverage decision, but this is essentially what it said. It would cover proton beam therapy if the target volume was close to critical structures, to avoid a 'hotspot', and if there was a previous irradiation, and also ocular tumors, skull based tumors, central nervous system tumors, primary hepatocellular carcinoma, pediatric central nervous system tumors, and pediatric head/neck tumors. Coverage would be considered investigational in other areas.

In providing a summary of the guidelines, most of these are all expert opinion combined with literature review. The National Comprehensive Cancer Network says that proton beam therapy may be appropriate for bone, CNS, head and neck, liver, lung, lymphoma, ocular, sarcoma, and thymoma types of cancer. The AIM Specialty Network, which is radiology, recommends it for CNS, ocular, and pediatric tumors. The American College of radiology recommends it for head and neck cancers, and it may be appropriate for lymphoma and prostate. NICE in the UK, the National Institute for Health and Care Excellence, recommends proton beam therapy for brain, spinal, paraspinal, and pediatric cancers.

So, I am next going to dive into what is, as you have read, a very complicated and a lot of study, and I am going to do my best to sort of distill that down into something that you can work with. So, first, I'm going to look at the adult cancer side of the literature. Again, overall, the quality of the evidence base is poor. It's mostly retrospective observational studies, including cohorts and case series, which are considered a moderately high risk of bias. Many of these have [inaudible] control that use older treatments or different types of radiation. Some of these studies had differential followup or differences in treatment groups, including different types of chemotherapy. So, it is really complicated to sort of sort out what the impact of it is. So, all these types of cancer listed on here, there are either similar conclusions to the last review, or there is no new data. Most of these areas have five or less new studies. I'd like to point out, there are two randomized control trials for liver and for lung and a quasi-RCT for prostate cancer. For bone, the RCT showed no difference.

This is one of the few really solid sorts of well-done trials in this literature. For prostate cancer, there is one RCT and 12 cohorts, or a few simple studies. The result of those seem to be that proton beam therapy may have lower accumulative incidence of GI and urinary toxicity in terms of grade 2, but not in grade 3 and 4, which includes more complications, like [inaudible] cystitis fistula. Then, breast cancer is another one that I think is worth pointing out. There is some question for women at risk of heart disease and proton beam therapy. Again, the literature is sort of mixed, and it is not a clear conclusion for that.

So, there are four areas where there are changes from the last report, that either have a different result, or they have a lot more data compared to the last results. So, I wanted to highlight these. So, for brain and spinal cancers, there are larger studies, and in the last review, the harms for proton beam therapy were less compared to conventional radiation. In this review, with the larger studies, the benefits and harms are similar. Second, for esophageal cancer, there is increased overall survival after one year and progression free survival is better. The review describes this as an incremental benefit. Also, with esophageal, there is more GI events, but the rest of the adverse effects are lower, especially pulmonary. So, this tends to move towards the positive side of this treatment for esophageal cancer. For liver cancer, there is an RCT that is under way that this is based on. So, this is early data, but overall survival, progression free survival, and local control are similar compared to transarterial chemoembolization, which was the comparator for this study. However, there were significantly fewer hospitalizations for complications. So, it seemed that people went to the hospital less and the complications that they had were less severe than those in the transarterial chemoembolization group. And then, for ocular, the ocular results really don't make very much sense. All of these studies are low quality. The five year overall survival in sort of the biggest study is lower with proton beam therapy, but there are fewer local recurrences. So, I'm not exactly sure what to make of that, other than most of these studies are quite small. Also, in one study, there are two bigger studies in this area, one study the visual acuity is worse, and the other one it's better with proton beam therapy. So, again, quite mixed, and some of the, one of the bigger ones is compared to brachytherapy, and all of them have moderately high risk of bias. There are 21 case series in this group, which, I think, leads to this degree of uncertainty for ocular types of cancers. There are various ocular cancers in these case series, and many had overlaps of the population that were included. So, it was really difficult to sort out, sort of what's the true benefit or harm.

So, based on all that, my recommendations are to cover with conditions if someone has esophageal or liver cancer, and these are new recommendations that are different from the last recommendation based on the current data. Then, also cover for brain and ocular cancer. This is already in our coverage criteria. Again, the evidence is thin in this report. It's a little bit stronger for kids, but I decided to sort of put it in there, since that's sort of where we are right now.

So, for pediatrics, I'm gonna do similar [inaudible]. For these types of cancer, there were similar conclusion to the last review with very few new studies. In general, there were six or fewer studies for each of these types of cancer, uh, and so it's difficult to tell if there's any change, but nothing stood out when compared to the last review. Then, the bulk of the evidence was really in pedestrian brain cancer, a number of different types.

Here, compared to the last review, it appears that there is an incremental benefit, in terms of decreased harms for proton beam therapy. This is largely driven by less counts of hypothyroidism. The overall survival in tumor recurrence is similar, maybe a slight trend towards favoring proton beam therapy. Then, the other set of new studies was in salvage for ocular tumors and salivary tumors. There is a small comparative study of each, which would label them insufficient evidence and low quality. There seems to be fewer grade 2 or 3 mucositis trends for the salivary tumor. So, that's sort of the trend of benefits.

The agency medicals directors discussed this a bit and are giving you two options to consider. The first is if you just look at the literature in this review and making your decision, then it's probably a cover with conditions, if there are central nervous system tumors, then I would put the brain and spinal paraspinal tumors into that category to what's currently covered. Or, you could also choose to cover all pediatric cancers. Again, there's the theory of proton beam therapy having less radiation to the tissues. So, proton beam therapy might prevent longtime future harms, but no study has really shown this yet. So, it's a bit of a theoretical question. With that, I am done. Are there questions?

Gregory Brown: So, when you said the Medicare National Coverage Decision was retired, that means there is no current coverage decision in place, and so it's local coverage decisions?

Judy Zerzan: Right.

- Seth Schwartz: I have a cost difference question. So, we're seeing the cost of protons coming down substantially over a fairly short period of time. I'm just curious, how does that compare with current proton therapy or current x-ray therapy in terms of expense for treatment?
- Judy Zerzan: That is an excellent question, and I don't know.
- Seth Schwartz: I guess I have one second question, which would be, we're talking about brain and CNS cancers, but there was some earlier talk about skull based tumors. I'm curious how those are classified. Is that considered separate from CNS tumors, are or those classified with skull based tumors?
- Judy Zerzan: I lumped them into that. Again, a lot of the studies are really small. So, the brain is a developed organ. It's all kind of around there. So, I thought about radiation to the brain as in one lump.
- Seth Schwartz: OK. Thank you.
- John Bramhall: Did you happen to know how many proton beam facilities there are in the state? It's a bit of a wonky question, but are there dozens or just half a dozen?
- Judy Zerzan: There is just one, and one for sort of the Northwest region. I think there . . . and this might be in our contractor's report. I want to say that there's 21 or 22 nationally, something around that.
- John Bramhall: And the only one that there is, is it the Northwest Facility? Is that where it is?
- Judy Zerzan: Yes.
- Sheila Rege: And if I could ask a question. So, you are . . . when you say on the pediatrics especially, or adults, you're including the chordomas and all that in as really a blanket brain in the brain, not sort of [crosstalk].
- Judy Zerzan: . . . [crosstalk] related. Anything close to central nervous system [inaudible].
- Sheila Rege: And, I didn't see anything about hepatocellular. Did you have something there? Do you have a feeling one way or the other or a recommendation.
- Judy Zerzan: I did. I put it in the cover with conditions.
- Sheila Rege: OK.

Judy Zerzan: I called it liver instead of HPC. Again, that was largely driven by this very well set up randomized control trial that is sort of underway, but it seems like there are fewer harms that are gonna be coming out by sort of a marked difference in hospitalizations for [inaudible].

Sheila Rege: And you are including both primary or metastatic in that?

Judy Zerzan: Oh, I can't remember. Yeah, it's just one, it's just one study. I could look that up, although I suspect our contractors might go into it.

Gregory Brown: Any other questions for Dr. Zerzan? Well, thank you, very much. Next is public comment. So, next is public comment. We have a number of people that have signed up to talk. So, we asked you to . . . we follow the agreed upon times. If there . . . also at the beginning of your presentation, we would ask that you disclose any sort of conflicts, including research funding, consulting funding, paying for travel, and things like that, so we understand what those potential conflicts are.

Josh Morse: Thank you, Dr. Brown. So, we have, right now, from what I can tell, we have two groups that have signed up in advance to provide public comment. The first group that we'll ask to address the committee is representing the National Association for Proton Therapy, and there are four individuals. We have agreed on a 20-minute timeframe for the four, and we will start with Dr. Chang. Thank you. Would you like us to divide your time equally, five minutes each, or?

Andrew Chang: Yes, please.

Josh Morse: No problem.

Andrew Chang: Good morning, and thank you, everybody, for having us to be able to come and speak with you a little bit about proton therapy from the public side. My name is Andrew Chang. I am a radiation oncologist. I practice in San Diego, California. In terms of conflict of interest, I am also a board member of the National Association for Proton Therapy, which is a group of individual centers that make up the association that helps engage the public and the media with their questions about proton therapy. My personal practice is primarily in pediatric cancers and breast cancers. I was asked to share a little bit about proton therapy from the clinical aspect of one who utilizes it at . . .

Josh Morse: I'm going to interrupt you.

Andrew Chang: I really apologize for this. We're having a little technical problem. We do have your slides. The committee has your slides in their binders. Are you able to get the slides up, Christine?

Josh Morse: Thank you, and I apologize for this.

Andrew Chang: We can go ahead. I'll get started, and you guys can take a look at the slides on your binders.

Josh Morse: OK. Thanks, very much.

Andrew Chang: No problem.

Josh Morse: And we'll get the technical folks to help us with that.

Andrew Chang: Yeah. I'm not quite sure. We've gotten . . . let me know if they're [inaudible]. So, I wanted to share more of a perspective of radiation doctors. We don't think about radiation, so much, as a drug, but we think about it as a tool, a physical device that we use to point the radiation in the area we want it to go. Radiation has been around for a long time. The first picture I showed is one of the . . . my favorite pictures, the first x-rays discovered by Wilhelm Rontgen physicist in 1895, and a picture of actually his wife's hand with her wedding ring on it. For that discovery, he won the first Nobel Prize in physics ever in 1901, and subsequently, the physicist in France by the name of Henri Becquerel and his colleagues Marie and Pierre Curie discovered that certain metals have the ability to give off radioactivity and that this discovery of uranium, polonium, and radium led to their winning the Nobel Prize for this in 1903. Shortly after that time, they started seeing what the biological effects of the radium, or these radioactive metals had on biologic tissue when one of these early physicists left a little piece of radium in his shirt pocket and developed an ulcer shortly thereafter. At that time, it was known that this radiation could potentially harm specific tissues. They started taking these little radium seeds and placing them on skin cancers and watching them dissolve, placing them on head and neck tumors, watching those go away, placing them within the cervical cavity for a woman's cervical cancer, seeing the cancer disappear. So, they know how this radiation has effects on biologic tissues. Now, it can effect cancers, but it also could affect normal tissues. So, they started seeing, what could we do to shape this radiation to give it just the area we want it to go. That does work very well for decades, and radiation therapy has been a staple of cancer treatment, since 1906, that first publication in Paris about [inaudible] implants. Most the radiation comes from the use of x-rays, which are the energy packets that go faster than the speed of light. What proton therapy is, it is a particle that allows

us to focus it and direct it to where we want it to go. This next slide shows a little bit about the history of it. This was first described by an English physicist by the name of William Bragg in 1904. And he won the Nobel Prize in physics for that in 1915. It was proposed to be used as a medical device in 1946. And the first use of proton beam therapy was on these research [inaudible] and treating patients with them. One of these first ones was done of a brain tumor in 1954. Shortly there afterwards, and this, of course, was the point of time of CT scan or MRI. So, you can not see inside patients. Then, in 1970s and 1980s, we discovered that technology. People said, now that we can see inside a patient, can we direct these beams, these precise beams where we want it to Google. So, the first one that was still specifically for medical purposes, not a research [inaudible] was built in 1990, and was the FDA approving device to utilize in 1989. So, the way I describe this in one of my many patients who ask is, I say, well you think about protons as another tool in our arsenal that we use to fight cancer. That's why having many patients see it or can understand it is, I say, one thinks about x-ray radiation, kind of, like, a shotgun that hits everything in the area, proton radiation would be like a target rifle, allowing us to pinpoint where that radiation goes. If you have a circle, or a peak . . . if you have a piece of paper with a circle drawn on it, you have a shotgun, you got some bullets inside that circle, some bullets outside. Target rifle, you can get all the bullets where you want it to go. Now, a piece of paper, it doesn't care how the bullets are getting there. It's simply, where are they placed. Similarly, in the human body biologically, it doesn't care if the radiation is getting there from x-rays or protons, simply where are they placed in there. So, I wanted to, a couple of thoughts about proton therapy as being experimental. We say it is not. There have been over 150,000 patients worldwide who have been treated with proton therapy, and the first patient treated with proton therapy was in 1954. The two largest medical regulatory [inaudible] in the United States consider it not experimental by treatment of cancer. FDA approved the first device in 1989. Medicare pays for proton therapy in the treatment of cancer. So, no [inaudible] thinks about it as experimental for the treatment of cancer. I do [inaudible], yeah. There are things proton therapy is experimental for. We're looking at using it to ablate seizure focuses in the brain. People are looking at using proton beam therapy to ablate ischemic pathways in the heart to prevent arrhythmias after myocardial infarction. They're not in the treatment of cancer. It's not something that [inaudible] experimental. I skipped a few slides, because I'm running out of time now. This is a study that I did for pediatric cancers with ten proton centers that were their first five years in operation, 2010 to 2013, basically showing that although CNS is making up the majority in the blue, at least 35 to 40% are non-CNS tumors in the pediatric populations. What is this amount of radiation? Well, does it mean when

you talk about this radiation dose? This grey is the amount of radiation. We talk about the numbers. It's small. You can see here what we see is the radiation that we avoid, although we don't have a study to say it does not do the effect, we can see [inaudible] the amount of radiation changes. This radiation is equivalent to about 100,000 CT scans. Now, we don't have any good studies showing 100,000 CT scans. It's [inaudible], but none of us would say, that's acceptable or, you know what, that's just fine. We'll watch it for a few years and see what happens. I mean, it's easy to see. Thank you, very much. And this is my last slide so, with that, 12 months later by one of my colleagues, a kidney 12 months with two patients with paraspinal Ewing's [inaudible] and atrophied. Then, 12 months versus normal. [inaudible]. Thank you for your time for allowing me to present a little bit from my perspective of how I use this tool.

Josh Morse: Thank you very much. The next scheduled speaker representing the National Association of Proton Therapy is Steven Frank. Dr. Frank.

Steven Frank: Thank you. I'd like to thank the committee for allowing us to come and speak. My conflicts, I am a PO1 investigator on proton therapy for head and neck cancer. I also have funding for H3 randomized trial from Hitachi, Varian Advisory Board, and I am a board member for the Alliance for Proton Therapy Access.

One other thing, I am a state employee of Texas, and I also am an advocate. So, I'm the short term deputy head for Radiation Oncology and Executive Director for our Particle Therapy Institute. Proton therapy is superior to IMRT in the following areas: Periorbital tumors, nasopharynx, paranasal sinus, oropharynx, salivary gland, and recurrent re-irradiation. Recently, the University of Texas system with a pilot with Blue Cross/Blue Shield provided thorough proton therapy coverage for all employees of the UT system in the state of Texas and their family. Why is proton therapy superior? This right here represents a proton therapy for an oropharynx patient. This is IMRT. This represents all of the unnecessary radiation that is exposed to the patient that can be eliminated by proton therapy. What is that translating to clinically? It translates into mucositis, edema, loss of taste requiring narcotics resulting also in inability to taste, therefore malnutrition and feeding tube dependency. With proton therapy, we can spare the intraoral cavity, and our studies show a 50% reduction in feeding tube dependency. What does that equate to? That 25 Gy is 12,500 CT scans, 5,000,000 dental oral x-rays, 25,000 times the general public annual limit, and 83% increased additional risk of cancer because of that extraneous dose. The beam path toxicities of IMRT have been well described. Here is the utilization of IMRT when it initially came out. You can see here some of the effects that occur on patients. And then, with PT

at the end of treatment, this is the neck, and we're able to maintain and spare the patient these toxicities. This is a young lady, a 28-year-old, recently pregnant that came to see me with a lacrimal gland tumor. This was the dose that we did with [inaudible] in surgery followed by postoperative external beam radiation of IMRT to 60 Gy. So, you can see the dose distribution. This is what her [inaudible] looked like three to five months after treatment, and this is what her [inaudible] looked like 11 months after treatment. With proton therapy, we are able to provide cure, clear vision [inaudible] by avoiding those anterior ocular structures and allow for prevention of orbital degeneration, which has been the standard of care. This has now been public well and described by our colleagues in the orbital [inaudible] group with eye sparing multidisciplinary approach to the management of lacrimal gland carcinoma. A randomized trial is underway and albeit, our data has shown from the standpoint of productivity and financial toxicity that proton therapy patients are able to achieve an 18% additional increase at two years of patient working following treatment. We do not see that with IMRT. With proton therapy, we see over 60% reduction of feeding tube dependency. With paranasal sinus, in these areas, no randomized trial was going to be done in the United States ever. There's not enough cases. We see survival benefits with proton therapy over IMRT. When we look at the University of Texas system, we have 14 institutions that make up the University of Texas system. We did a college study with them to be able to demonstrate the value of proton therapy. We were able to show when we use a radar plot with a scale here of higher costs higher up, that when you use proton therapy, you have higher costs with pharmacy, laboratory tests, internal medicine, emergency department, and diagnostic imaging while you have the incremental costs additionally with proton therapy. This all showed a high value proposition. It was further demonstrated by looking at the projected cost of the hybrid study of 748,000 to the UT system. The actual amount was -426,000, which showed an equivocal difference in cost savings of over a million dollars. This translated to a cost per life of \$2.38 projected to an actual of -2.29, which was a total of -\$4.68, which is to the benefit by utilizing proton therapy to help spare the toxicity to our patients.

Overall, we see proton therapy is clinically superior to IMRT. The University of Texas employees and families will have access through utilizing Blue Cross and Blue Shield. Thank you for your attention.

Josh Morse:

Thank you, Dr. Frank. So, our next scheduled speaker, representing the National Association for Proton Therapy, is William Hartsell.

William Hartsell: Thank you. I'm Bill Hartsell. I am at Northwestern Medicine Chicago proton center. I am the medical director there, and my travel today will be reimbursed by the Seattle proton therapy center. So, I know this is an awesome responsibility to determine which technologies are important and which should be covered. It's a difficult task, and there is a tremendous amount of data, which has been reviewed; however, I think that implementing the proposed coverage recommendations would be a giant step backward compared to the rest of the world. The primary problem is that this policy is a one size fits all policy, and it lacks clinical perspective. What you'll hear from us today is that not every patient needs proton therapy. There has been discussion about trying to remove bias by selecting only certain types of studies. The problem is, this doesn't work, because the patients we seek for proton therapy are already highly selected. In my physician practice, we treat about 5,000 new patients annually with radiation therapy, but only 10 to 12% receive protons. The rest receive x-ray or brachytherapy. We are a tertiary or quaternary referral center. So, we actually get a lot of patients coming in specifically for proton. So, that number is actually probably less, in general. Many of these patients are referred by other radiation oncologists, because they cannot be safely treated with standard radiation therapy techniques. So, this new policy recommendation to cover only for these sites in adults takes away decision making from the patients and their doctors. It's a blunt instrument, which has no nuance. So, the astromodel policy, which was mentioned by Dr. Zerzan, the NCCN policies for multiple other countries, including the Netherlands, U.K., and Canada. I [inaudible] London and Amsterdam rooms. I guess we'll bring them in, they take that nuance into consideration to allow for clinical judgment. So, in the Netherlands, a small country, they have three proton facilities and a fourth is opening soon. They've decided to base their treatment decisions on modeling studies, not randomized control studies. They see which individual patients will benefit from treatment rather than making broad categories which say include or exclude. The U.K. now has multiple proton centers and are treating wide indications than you may see in the proposed policy, depending on how you decide.

So, some specific examples, lacrimal melanoma review ignores a randomized trial of particle therapy versus plaque brachytherapy at the University of California San Francisco, which was published three years ago. They used helium ions instead of hydrogen ions, but they are both relatively small, heavy ions. The UCSF data with protons is the same as with their helium ions. That randomized study showed that three times as many patients required enucleation after treatment with brachytherapy compared to the particle therapy. In addition, plaque brachytherapy is not recommended for thicker tumors, larger tumors, tumors that are too close

to the optic nerve. So, this may explain your question about ocular melanomas. Why is survival worse, sometimes, in the patients who receive protons? It's because we're treating the bigger tumors that can't be treated any other way. The policy analysis doesn't make this decision. They use a cost benefit analysis, which also does not include things that would be done by any difficult patient. For example, if a patient has an enucleation, typically they don't just go around with an empty eye socket. They have a prosthetic. That's not included in that analysis. So, if you look at proton therapy, that's actually less expensive than the other two treatments. So, I was pleased to see that Dr. Zerzan is recommending continued coverage of the ocular tumors, despite what the report said.

I recently saw a young woman, she was in her 40's. That's young to me anyway. She had breast cancer with positive axillary nodes and needed comprehensive radiation therapy to the chest wall and nodes following her chemotherapy and mastectomy. She was referred to me, because she also has pectus excavatum. So, the radiation oncologist who saw her initially performed a treatment plan with IMRT, but the dose to her heart and lungs was unacceptably high. She was referred to us to be treated with protons, because we were able to give the treatment with minimal dose to her heart and lungs, and this proposed policy would not cover her treatment. Another of our patients was a young woman in her early 20's diagnosed with a huge rhabdomyosarcoma of the mediastinum. Again, referred to us from a radiation oncologist several states away from our center, but because their standard treatment gave unacceptably high doses, she didn't want to treat the patient and referred her to us. So, our treatment gave significantly lower doses to her heart, lung, breast tissue. This proposed policy puts this in the non-coverage for all other group.

So, these policies look only . . . excuse me, the analysis looks only at a short time into the future and consideration. The big advantage of proton is in sparing the normal tissues, which may reduce the risk of longterm complications, lowering the risk of heart disease in the young woman with breast cancer, lowering the risk of radiation induced breast cancer and lung problems in a patient with a large mediastinal tumor. So, many of the patients we see with protons are younger with large tumors and unusual diagnoses for whom no other good treatment experienced option is available. So, I would suggest adding the nuance in with two policies in the astromodel policy, which could be used as a guide; one a proton based technique, which would increase the probability of a clinical meaningful normal tissue toxicity by exceeding the integral dose base associated with toxicity; two, the same or immediate adjacent area has been previously irradiated. In addition, my recommendation is to accept the second

pediatric recommendation from Dr. Zerzan and cover all pediatric cancers. Thank you.

Josh Morse: Thank you, Dr. Hartsell. The fourth person representing the National Association for Proton Therapy, and if I have this wrong, please correct me, this is Dr. Keole. And are you with NAPT or SCCA?

Sameer Keole: I'm with, sometimes I think I'm with neither. I'm with the Mayo Clinic. Actually, Mayo was going to cover the cost of travel, but SCC was kind enough to do it. So, my name is Sameer Keole. I am a radiation oncologist at Mayo Clinic. Travel is being covered by SCCA. The reason Mayo, when we ran it through the Mayo chain that they wanted me to speak, is that we were concerned about the walk back in coverage guidelines. There was a lot of, in our opinion, errors made in the way the current data is analyzed. So, we thought it was important that I come here.

At Mayo Clinic, we have a 155-year practice of innovation and incorporating new technologies, which at the time, are met with some skepticism. This starts with the microscope in 1871 going to the CT scan in 1971 and proton beam therapy, which was, we installed two centers after a decade long evaluation of the technology where it was and where it was going. Mayo is a very conservative organization. So, our conclusions were that not only is it safe and efficacious, but also there was significant cost-effectiveness, which I know you're taking into account. I thought it was important to remind everybody, we talk about randomized trials. NCCN, which is the leading organization for establishing guidelines 6% of the recommendations are made on level one evidence. So, the majority of the guidelines come from non level-one evidence. If we relied on level-one evidence in oncology, we would never treat a patient. So, we do have to use clinical judgment.

The clinical focus is on pediatrics in young adults, and that's really, again, what brought me here personally. I'm very concerned about non-CNS, but also lymphomas. So, radiation therapy to the heart, lungs, breast, and thyroid when you treat the neck is bad. I don't think we have to . . . and not even necessarily in the radiation literature. That's throughout the literature. We know from patients who have a relatively low dose, and in patients when used x-rays for tinea capitis and other nonmalignant indications years ago, we now see significant side effects later on. In heart, we now know that patients who receive relatively low doses to the valves show up in their 40s and 50s with valvular dysfunction. We published this at the University [inaudible] in 2005 and JAMA. It was the first publication. These patients get lost to really most systems, but it's critical for longterm survivors. That's a big differentiation to be between a state plan that's

evaluating state employees where you have to take the longterm view and commercial plans, which honestly only look at a three to five year window, because the plans roll, the patients roll over.

In breast, we know that there is a markedly increased risk of breast cancer incidence in especially women under the age of 25 who received radiation to the breast tissue. In thyroid, doses as low as 5 Gy increase the risk of thyroid malignancies 15-fold over the patient's life, and those cancers are much more aggressive. They have a much higher propensity to be anaplastic and not your garden variety thyroidectomy, drink some iodine.

There is significant longterm savings with proton therapy, and I think that's, again, I want to emphasize, that, to me, is a big difference between, I think, your responsibility and those . . . if you're in a commercial healthcare plan, your responsibility is really for three to five years and really shareholders. For you, I think, it's to the citizens of the State of Washington, because somebody has to pay for these late effects, but even then . . . so I can't speak for SCCA, but at Mayo Clinic, the woman with advanced breast cancer who comes in, we have an ability to integrate treatments and do something called simultaneous integrated boost. Dr. A and Dr. Rege, I am sure, could explain this in greater detail in closed session if you need it. So, we can actually treat many patients in shorter courses than you could with x-rays. At Mayo Clinic, that woman with advanced breast cancer who comes in, the treatment, the global cost for protons versus x-rays is actually 12% cheaper up front. Let me repeat that. It's cheaper, in terms of cost, for us to treat a patient with proton therapy at Mayo Clinic with fee for service, as opposed to x-rays. That also gives us superior target coverage, 75% less lung dose, and 95% less cardiac dose. So, the significant longterm savings. The last point is that the patient that Dr. Chang showed, I'm not sure you could appreciate it, the two patients side by side, the Ewing, those were my patients in 2006, three months apart. I could spare the kind of, the ipsilateral kidney in one patient, couldn't in the other. What was the difference? The patient actually, the creatinine went up to over 3 and is now that patient is on longterm ACE inhibitors who received x-rays. There is absolutely no kidney deficits in the patient who received protons. That's not really captured, but somebody is paying for that decreased renal function. So, that concludes my comments. Thank you for your time and attention.

Josh Morse:

Thanks very much. OK. So, our next group of speakers is representing the Seattle Proton Therapy Center, I believe. Again, correct me if I'm wrong about that. The first one is Dr. Bloch that I have listed. How many speakers does the proton therapy center have, four? We'll do five minutes each, Chris. Thank you. Same as the other group. Thank you. What order would

you like to go? Who is next? OK. Thank you. Did you want us to time five minutes each or? OK. Thanks.

Ramesh Renan: After all this, I . . . my slides are indeed first. Let's see. Yes, they are. OK. So, my name is Ramesh Renan. I apologize. I have a bit of laryngitis today. I'll try to do my best to convey my message. I am a professor and interim chair, as well as medical director of the proton therapy center, the one proton therapy center that we have here in the State of Washington. I did derive no direct salary from the proton therapy center, as far as conflicts of interest, but I do get an administration stipend from the University of Washington for my role, as the medical director. I, like, Dr. Rege, have also attended national meetings, which almost in all likelihood have been co-sponsored by vendors who deal in the business of proton therapy, and those are my conflicts.

So, I think it's very important when you embark on an Enterprise, such as this, as a committee, that we start with a common fact basis. I would submit to you that these facts that I am going to present to you are facts. These are not of question. These are not in doubt. There is absolutely no disputing the notion that there is no benefit through radiation to healthy tissue. There is nobody in this room that would dispute that notion. Nobody would willingly exposure their healthy tissue to radiation.

Second, there is also no dispute that proton beam therapy reduces the radiation exposure to healthy tissue when compared to x-rays and potentially every single patient that you would do a plan on. The magnitude of that reduction can be smaller. It can be 10 to 15% reduction. It can be several hundred percent reduction in terms of the reduction of x-ray and radiation exposure to healthy tissue, but there is always a reduction. So, the question is, what is the magnitude of that benefit and proving the magnitude of the benefit for the reduction of harm from the radiation exposure to healthy tissue is not something that you can quantify through a prospective clinical trial, which is a critical part of your evidence gathering here, prospective clinical trials are randomized trials. If you asked us to do a randomized trial to compare the value of a low dose CT scan versus a high dose CT scan, which both of them, let's say, give you the same image, you would never get the results that you want through a randomized trial. You'd never be able to quantify that, because your time horizons are too long. So, it's a very important to know the limitations of the process that you used here. So, how do we, how do we address this, as radiation oncologists. Well, our practice, radiation oncology, is to reduce radiation exposure to normal tissue. You use the ALARA principle, as low as reasonably achievable. This is a standardized radiation safety practice accepted around the world. How do we quantify that magnitude

of reduction of radiation exposure? It's through dosimetric comparisons. We do this every day in our clinic. When we . . . how do we decide whether we're gonna use IMRT or 3D Conformal or protons for a given patient? We run a plan, and then we see where the dose is going. Wherever we are able to get the best dose distribution, in other words, reduction of dose to the healthy tissue while maintaining the dose to the tumor, that's the plan we go with. I would make sure you are all aware that you excluded all of these dosimetric studies from your evidence generation here. These studies were excluded from your process. We believe that's a fatal flaw in the process that you're marking; however, we also recognize here that popular resources are refining.

So, we always have to look at cost in terms and value in terms of not only outcomes but also costs. We have to be good stewards of healthcare resources. That's why, at our proton center, we had actually very rigorous review of every [inaudible] patient who was considered for proton beam therapy. We had five different layers of peer reviews. So, it's not straightforward that if a patient . . . the vast majority of patients are referred for proton therapy do not get proton therapy, because somewhere along the way in the peer review, we feel that it's not appropriate or they are better served with another modality. I don't think this is true in any other anti-cancer intervention, this many layers of peer review, and we have that because we recognize that this is a finite resource. So, who do we believe benefit from proton therapy? Pediatric patients, mind you, it would be unethical to conduct a randomized trial in pediatric patients of standard x-ray therapy versus proton. You could not do that. Why? Because if you look at that radiation exposure that you get with an IMRT plan versus proton, no parent would subject their child for that. So, what is the basis for proton being an accepted standard of care for pediatric patients? Is dosimetric comparisons, and I would say in a variety of other [inaudible], such as ocular cancer, head/neck cancer, there are emerging data, and we are committed to evidence generation at our center; 70% of our patients who are enrolled . . . who are treated are enrolled in a clinical trial or on a prospective data collection registry. Compare that to any other cancer intervention . . . patient cancers average only about 3% of patients who are enrolled in clinical trials, and 70% at our center. So, we're committed to evidence generation. We've had over 100 patients enrolled in prospective clinical trials, since 2013. What is the challenge with these trials, though? Well, we need coverage. Right? If we don't have coverage, it's very hard to get patients enrolled onto clinical trials, and I would show you that my final slide . . . I would show you that your coverage recommendations right now are going to put you way out of step with any accepted national consensus guidelines for utilization of proton therapy. And I think ultimately, this may end up being a real

challenge for the citizens of Washington State, as this is the only center within 800 miles and it leaves them kind of wanting for a resource that's quite important for a small subset of the patients that we have here. So, I thank you for your time.

Josh Morse: Thank you, Dr. Bloch. So, to Dr. Emoian.

Ralph Emoian: Alright. Thank you, so much. My name is Ralph Emoian. I am an associate professor of radiation oncology at the University of Washington, and I am the primary pediatric radiation oncologist. At least through the University of Washington system, I probably create about 50 or 60% of the children who need radiation treatment in the State of Washington. My disclosures are in the slide that I am employed by the University of Washington, but part of my practice is at the proton center. I say it's part of my practice, because I treat a lot of patients, including some children, with protons. So, it's always individualized decision. I also want to emphasize that an issue that was raised by previous speakers. Almost all of my patients are [inaudible] either in combination between a medical oncologist and a radiation oncologist, or directly by radiation oncologists. So, when they are referred to me from outside the University of Washington system, whether it's from Spokane, Tacoma, Olympia, usually their radiation oncologist has already made a decision that based on her or his expertise, proton radiation would better serve a patient than if they were to treat them closer to home. Sometimes, in my further analysis, I go back and say, you know what, actually based on my experience, I think proton would be the right choice, and usually there has already been a decision locally that proton would be a better choice based on a radiation oncologist's opinion.

There has been a lot of discussion about randomized trials. I wanted to share with you my perspective, as a pediatric radiation oncologist. This is imaging showing various craniospinal plans you see in other pictures similar to this. We are aiming at all of the spine and all the brain. I feel, in order to adequately [inaudible] for a randomized trial that would involve protons or photons, I would be able to show these pictures to the patients. Blue is good. Blue is areas that don't receive radiation. I'd have to be able to tell a family, I want you to allow a randomized trial to decide whether your child's heart, lung, liver, kidney, valve, uterus, ovaries, thyroid, a randomized decision about whether they were going to be exposed to radiation knowing that everyone in the world would agree that radiation exposure shown in any of these organs is not a good thing.

So, how do we in the pediatric oncology community approach this question? So, the largest research organization in the United States for pediatric cancer, the Children's Oncology Group, we participate in almost

all of their trials, and those trials allow a clinician decision about what is the best way of treating the patient. Based on the clinician's decision, they are enrolled . . . either to be treated with protons or photons, and there are retrospective reviews of those patients to see what outcomes will come. Now, part of the challenge, also highlighted by others, is that the patients I treat are ones who have the longest time to experience the longterm side effects of radiation. We're hoping eight, nine decades in some cases. That is a long time to accrue the data. So, we have retrospective reviews that we have that seem to suggest that patients have less side effects from proton radiation. Let me highlight the last thing, and then I'll cede the rest of my time, which is, what is the coverage situation for proton. As you already saw in some of the summaries from other presenters that protons are covered for most pediatric malignancies, CNS or otherwise. I have to say, from my experience, I've been in practice at the University of Washington for eight years, since the proton center was open. I think we've had two or three patients decline proton therapy from all payer types, not just in the State of Washington, but also from surrounding states, because we serve patients from all of [inaudible], from Oregon. We also serve some international patients, and it's really quite extraordinarily rare that anybody gets turned down for proton therapy, regardless of whether it's a CNS tumor or otherwise. So, if we were to step back and no longer allow proton therapy for all malignancies, that would certainly take the State of Washington to a different place than pretty much almost all other insurers in the region, and also in British Columbia, as well. So, thank you, so much, for your time.

Josh Morse: Thank you.

Janna Friedly: Question for the vendor? I'm hearing that the safety profile, in your opinion, is better. I'm hearing about the cost-effectiveness, and I'm hearing you say that sometimes you say no protons are preferable. Can you give me some examples of when you send somebody back for photon?

Ralph Ermoian: Sure. Thanks for asking the question. There's a couple examples. One is, at the University of Washington, one of the preparatory regimens for treating a patient who is getting ready for a stem cell transplant is the total body radiation. We are deliberately targeting the entire body. We don't want the beam to stop. So, that's a perfect situation in which we say, there really isn't a role for protons, because we don't want the beam to stop. The other clinical decisions we make are, if the patient has the diagnosis where we are treating with curative intent, but we know that it's extraordinarily unlikely the patient is going to survive a year or two or three, and I can think of a terrible brain tumor called diffuse infiltrate

pontine glioma. That is a tumor which we treat with curative intent, but the patients are typically declining by the day, and they are unlikely to live, unfortunately, more than a year or two. In those cases, often we say, really, what's best for that patient is to start the therapy immediately rather than travel, and allow them to be closer to home. So, when I get asked about a patient with that tumor, I often say, I really think it's probably in the best interest of the patient to stay closer to home. OK. Thank you, so much.

Josh Morse: OK. The next speaker representing the proton therapy center is Dr. Bloch.

Charles Bloch: So, I'm employed at the University of Washington, and I provide clinical support at the proton therapy center, although I'm not paid directly by them. A little bit about me, I've been a medical physicist for over 25 years doing proton therapy throughout that entire career. I'm a University of Washington employee. I said that, and I am a head/neck cancer patient. This is a PET scan of me. The bright yellow areas are the cancer disease that I was diagnosed with in 2016. I had proton radiation therapy in January through March of 2017 and have been cancer free, since then. This is my treatment plan. You've heard about how we use computers in the simulator where the radiation is going to go. I don't know if there's a pointer here, but the colored lines show where the dose ends up inside the patient, but more importantly, it shows where the dose doesn't end up. When the physicians prescribe dose, it goes [inaudible] work on modeling where the beam is going to go, and the [inaudible] tell us those limits of the other structures for things that they are not treating. This is what we do. We spend all of our time trying to limit the dose to these other structures. So, the idea that we need a clinical trial to say the dose to these other structures is bad never comes into play in our practice. We know that if you radiate the salivary glands to these high levels, that they will die and the patient will not have saliva. They won't be able to eat. They won't be able to talk, and a number of other problems. So, the good news in my plan is, all the radiation was combined to one side of my neck, just this side. This salivary gland was partially spared. This salivary gland was 100% spared, and I have very few side effects from my treatment. It turns out, and as a medical physicist, I don't know all the side effects, but it turns out when you lose your saliva, you start losing your teeth, as well, because the saliva has bacteria in it that helps keep your teeth and your gums healthy. So, in the two years since, I've had no cavities, but unfortunately, they decided not cover my proton therapy treatment, and this is really kind of embarrassing. I mean, the University of Washington says to the public, we provide healthcare anywhere. Then, they say to their employees, but not for you. I mean, this really hurts. The importance of quality of life is just . . . you can't take that into account easily. So,

people grow up, reduce risk of secondary cancers, reduce risk of side effects and other associated health costs. I didn't have to have a feeding tube. I still have salivary function. I have a reduced risk of swallowing dysfunction, which is something I didn't know I would have until after my treatment, but it turns out you lose some muscle control and things kind of go down the wrong pipe every day, and reduced risk of aspiration pneumonia. I continued working during my first three weeks of radiation therapy. So, I was in the clinic working on other treatment plans. Then, when it was my time, I'd go downstairs and get treated. Then, I'd go back up to my desk and continue working for the rest of the day. Near the end of my treatment, I had to take some time off, but I returned to work fulltime two weeks after the completion of my radiation therapy, very minimal side effects to this.

This is a picture of me at the very end, my last day of treatment therapy. The banner there was made by my daughter who was five years old at the time. The prospect of being able to continue a healthy and normal life is important, not just to me but to my family. This is what this quality of life is about. That's all I have.

Josh Morse: Thank you, Dr. Bloch. So, the next speaker for the proton therapy center is Dr. Zeng.

Jing Zeng: Good morning. I'm Jing Zeng. I'm an associate professor of radiation oncology at the University of Washington School of Medicine Department of Radiation Oncology, and I am also the associate medical director for the proton center. As my colleagues have stated, I am not paid directly by the proton center, but I am paid by the department of radiation oncology.

I thought we would spend a few minutes together, I believe later this morning you're going to go more into depth into the actual data that's been generated, but I thought we would spend a few minutes together looking over what the current data proposes, as a coverage policy, and how that aligns with what is currently being done nationally, as well as internationally. One of my colleagues very briefly showed this coverage policy before summarizing what private payers do across the country, as well as what our . . . so this is the 2014 coverage policy from the Washington HDA, as well as what we would be estimating the coverage policy would be based on the evidence report that's generated, as well as what Astro recommends in third party external reviewers. As you can see, if we were to go by the evidence and not cover non-CNS pediatrics, we would be pretty much the only policy to not do so. To provide some context, since the center opening approximately in 2013, in total, we have treated probably about 130 patients who would no longer be covered, if

the coverage policy were to be changed, based on the current draft report. So, for example, we treated 19 pediatric patients that were non-CNS. We treated 81 patients who were adult brain CNS patients, as well as 10 patients with ocular melanoma, as well as 21 patients who are re-irradiation. The sum total of treating those 130 patients over the past five years, I think the word cost has been mentioned quite a bit, the sum total of treating those 130 patients over the past five years, if you were to compare it to IMRT, because presumably these patients would still have received radiation, was less, about \$80,000. So, that's less than a \$20,000 a year difference for us to have treated those 130 patients who would no longer have coverage under the new policy guidelines. The evidence report would suggest that when you are looking at what the disease site that you're hearing from us the most about, for example, non-CNS pediatrics, adult brain, as well as, I think in the oncoming years, we're going to see major changes in coverages for head and neck, due to the immense amount of data that is being generated for improvement, in terms of outcomes, especially toxicity, quality of life for head and neck tumors. We're going to see those coverage policies change, as well as for ocular melanoma, as well.

So, if we were to summarize what we think would be a reasonable coverage policy for the patients and employees in the State of Washington, I think we keep being asked for evidence generation, we believe in that, but for us to achieve that, you have to cover patients. So, we would suggest coverage for all patients that are enrolled in a prospective clinical trial or registry, which is consistent with your coverage policy for IMRT. We would recommend coverage for all patients with ocular melanoma that are referred to our center and considered to be appropriate on multidisciplinary review to be appropriate for proton therapy. We would recommend covering patients with CNS tumors, all pediatric patients in consistency with the thought that less radiation is better for you, especially when you have patients that are going to live for decades, patients who are undergoing re-irradiation. Again, a lot of the time, they are being referred to us by radiation oncologists, because it's not possible to treat them with regular radiation, as well as tumors that are in close proximity to a number of organs at risk, such as head and neck cancers, left-sided breast cancer, as well as young patients that are no longer pediatric but are expected to live for decades with their lymphomas. I believe that's actually the end of my slides. Since I do have a little bit of extra time allotted to me, I'm certainly happy to take any questions from the committee members if there are any, as well. Thank you for your attention.

- Mika Sinanan: So, one of the previous speakers alluded to the fact that 70% of all patients coming through the proton center are on studies.
- Jing Zeng: Correct.
- Mika Sinanan: So, will those studies include the kind of longterm safety data, longterm side effect data that many speakers have alluded to but are not captured in the available data in our analysis?
- Jing Zeng: Sure, so I think we have opened at our center a registry trial called the PCG registry trial, and that is a national effort across quite a number of the proton centers, especially ones affiliated with academic institutions to try to generate this evidence that's being asked for where we actually look at who are the patients we're treating, and what are their toxicity rates, and we're trying to follow these patients. When you ask us for 10 to 20 year data, of course, that requires 10 to 20 years to generate that data. So, yes, that is one of the . . . you're seeing publications that are coming out with short-term followup, because that's how long the centers have been open, but our goal would be that, yes, five to ten years from now, you're going to see studies with 10 to 15 year followup about what those longterm toxicity rates are. I think otherwise, I would also mention that when you're talking about kind of getting patients enrolled in a clinical trial, we also have quite a number of randomized clinical trials that are open at our center, as well, looking at proton radiation versus IMRT to do that evidence generation of randomized trials. Even patients on those trials are not covered. That makes it difficult to approve to those randomized trials that the insurers are asking for.
- Mika Sinanan: Thank you.
- Jing Zeng: Other questions?
- Josh Morse: Thank you.
- Jing Zeng: Then, I thank you for your attention.
- Josh Morse: So, that concludes the signed up public commenters. Do we want to check the phone?
- Gregory Brown: So, there are no more signed up here. OK. Can you unmute the phone then, and we'll see if anybody is online? Hello, this is Greg Brown. I am chair of the Health Technology Clinical Committee. Today, we are doing a rereview of proton beam therapy. We are wondering if anybody is online that has public comment that they would like to make? Just in case, if you

are trying to get on, remember you may be on mute if you muted your own phone. OK. I am not hearing any other public comments. So, we will then move to our contractor presentation. Do we . . .

Josh Morse: We should take a break.

Gregory Brown: . . . oh, sorry. I was going to say, break time, and then the contractor presentation. OK. Thank you.

I think we are ready to reconvene. OK. Dr. Skelly, we are ready for your presentation.

Andrea Skelly: OK. Thank you. I would like to start by thank those individuals who assisted in the preparation of our report who are listed on the first slide. Did I miss something with the first slide? There we go. OK. So, moving forward, I hope, where do I need to point this thing? There we go. I think we've got it. OK. So, the purpose of our report was to objectively systematically review and clinically appraise new evidence for proton beam therapy using accepted standardized methods for systematic review, and you can see the objectives here. Consistent with the 2014 report, our report focused upon comparative studies for this updated report.

Most of you are familiar with the background on the prevalence of cancer. It is estimated that at least 1.7 million new cases are diagnosed annually, and cancer conditions are responsible for over half a million deaths per year. The cost for cancer treatment, of course, is not insignificant. There are a number of tumors that do respond well to radiation therapy. Some of them are included her, including the prostate, head and neck cancers, and nonsmall lung cell lung cancers.

About half of all cancers, or more, benefit . . . the patients benefit from sort of radiation therapy in the management of their disease. Radiation therapy could be used for a variety of different purposes, including curative purposes for a tumor, postoperatively to shrink tumor size, prevent recurrence or spread of tumor, or for palliative treatment. Most common forms, again I'm only going to spend a little bit of time, because I'm sure the public comments have given a much better overview of the radiation therapy world, but external beam radiation therapy is delivered externally using a machine that produces an aim high energy beam directly at the tumor from outside the body. Brachytherapy is another common form of radiation therapy that is delivered internally using radioactive materials.

The goal of radiation therapy, as you heard, is to keep the exposure as low as possible, damaging the cancer cells but sparing normal tissues and organs at risk. Historically, things have evolved substantially in the radiation therapy world over the past number of decades. Two-dimensional radiation therapy was allowing a visualization of the tumor in two-dimensional plane to evaluate the location and dimensions of the tumor. More recently and more standard of care had become using three-dimensional conformal radiation therapy, which uses advanced imaging technique, and the importance is to identify critical organs at risk and to match the beams to the shape of the tumor from all directions.

In terms of classification of different types of external beam radiation therapy, it can be classified based on the type of particle used. You've heard about intensity modulated radiation therapy, and it can be altered to let the intensity near those sensitive organs and deliver high doses to tumor volumes. It may be done with either protons or photons. Stereotactic radiosurgery is another form that delivers protons, photons, gamma rays, and fewer fractions of higher doses. I only mention it, because it's one of the comparators in the studies that we've included. There are different types of laser delivering proton beam therapy, including passive scattering, uniform scattering, and pencil beam scattering.

As you've heard, protons have different radiation physics principles. Photons are neutrally charged and are lightweight compared to protons, and they're characterized by a high deposition of energy near the body surface, and the exponential decay you see in the red line there. Proton, by contrast, are heavy particles that are charged. They deposit peak radiation energy more precisely at or around the target of radiation. Then, there's a sharp decline after the target area known as the Bragg peak. Again, my colleagues from the radiation therapy world have explained this probably in better detail. You [inaudible] there's a greater dose of radiation therapy delivered to the target neoplasm, but mitigating unwanted radiation therapy to surrounding tissues. There is a brief look at the distribution of radiation for 3D conformal radiation therapy, IMRT, and proton beam therapy. You can see that there is a difference in the distribution of doses based on this.

Radiation therapy delivered by proton beam therapy requires a specialized facility. There are 27 within the United States, I understand, and five under construction. This is from the Seattle Cancer Care Alliance proton beam therapy area. Then, by contrast, photon beams require still specialized, still with these, but are very different in terms of their requirements for physical containment and physical properties to generate the beams.

In terms of harms of radiation therapy, the side effects [inaudible] occur when normal tissue is irradiated. They vary in effect based on a variety of factors. They depend on things like location of the tumor, the field of radiation, hyper-radiation, the method of delivery, the timing of the treatment, the doses per fraction, total doses, a person's overall health and comorbidities, and of course the patient's age is very important. Children are a special case, because of the developing tissues, and the ways that need to be protecting them from excess radiation extension, because they will be living longer lives presumably.

There are some uncertainties around the radiation distribution that need to be considered. I'm not gonna go over them in detail, but the assumption the biological effects of protons and photons are roughly equivalent has been challenged in some literature. There is more uncertainty around tumors that are at a deeper tissue depth and those would be more in adults and, in fact, is of other particles such as neutrons, may produce some additional radiation dose.

Mika Sinanan: So, before you get off of that issue, I thought . . . could I ask a question of our guest speaker at this point? One of the key questions that's raised by that prior . . . this slide . . . in the first bullet and by some of our speakers is that protons and photons are essentially the same, except that the . . . it's a way of focusing energy, but that the characteristics and the effect of the energy is no different at the effective site. It's simply less spread, more focused, more defined. More precisely defined way of focusing energy, as opposed to, there's also a difference in the effect of the energy, that it's a different type of energy, that it has a different effect on the tissues. So, my question with this question of uncertainty that is raised is, do you have a perspective about that?

Smith Apisarnthanarax: So, I actually had a question myself. I wasn't really sure what was meant by less certainty. I think historically if there were any differences biologically between the two, it was thought to be minimally clinically relevant. Certainly, if there is any uncertainty, it's not that it's less effective. If anything, it might be more effective, but there is ongoing data to try and sort that out. I also wanted to, since we're on this slide, because I think it does raise concern on the last bullet point about possible safety with the generation of neutrons. So, it is true that passively scattered proton beams can generate neutrons, but passively scattered proton beams aren't really used clinically anymore in most proton centers. So, I think that kinda does speak to the current relevant safety issue.

Mika Sinanan: And then, just as a followup question, on the slide that talked about delivery techniques passive scattering uniform scanning, pencil beam scanning, are those differences relevant to any of the studies that we're talking about? Are those characteristics of one device versus another device or can you turn one on and turn it off within a certain type of device? Can you comment about that?

Smith Apisarnthanarax: So, each machine that is delivering a proton, typically, it's to one or the other. In terms of passive scattering, uniform scanning, or pencil beam. Think of those deliver techniques as just how you manipulate the protons. They're all protons being delivered. They're generated differently, and they're manipulated differently. So, pencil beam scanning is the most advanced form of how we deliver proton beam therapy. Historically, most of the data that's been generated is with older techniques, mainly because the technology to deliver the most advanced form of protons, which is pencil beam scanning, is relatively new, but it's equivalent . . . the way I think about it is, how you manipulate x-rays. You can do it very conventionally with 3D formal where you don't really manipulate and shape the beam, as well. PBS allows one to shape the protons much like we can use IMRT to shape x-rays.

Mika Sinanan: So, every patient treated now at the proton beam center uses pencil beam scanning. Is that right or?

Smith Apisarnthanarax: Not . . .

Mika Sinanan: [inaudible] back and forth?

Smith Apisarnthanarax: . . . within each machine . . . so, we do have one machine that has uniform scanning. The other two have pencil beam, but within each room, we don't really switch back and forth, but we . . .

Mika Sinanan: But the characteristic of the machine?

Smith Apisarnthanarax: . . . within the room that's conditioned to deliver.

Mika Sinanan: And do you choose one or the other in terms of treatment?

Smith Apisarnthanarax: Yes. It's the decision that's made between the physician and the whole team with physics, in terms of which beam delivery technique is the most appropriate, and also resource allocation, in terms of what's available in each room.

Mika Sinanan: So, my final question is, since you said that the pencil beam is the most advanced form, it's the most recent. We have the least data on it. The effect of a pencil beam would be to concentrate the energy even more precisely than the previous versions.

Smith Apisarnthanarax: Correct.

Mika Sinanan: So, if anything, the benefit would be at least between the non-treated surrounding tissue and the treated tissue, the dosimetric difference would be greater with pencil beam. Is that correct?

Smith Apisarnthanarax: That is the thinking. Yes.

Mika Sinanan: But we don't have the data yet, because it's too new?

Smith Apisarnthanarax: Well, I mean, we have data, but I think the historic data that has been previously published, the majority is with older techniques, but I think the data are coming out.

Mika Sinanan: Thank you.

Sheila Rege: And to continue on that, because I think that was very good. Mika, it's kind of like 2D with photons versus IMRT, you know, kinda shaping the beam, but talk to me about neutrons. In pencil beam, is it negligible to where it's completely discounted, doesn't have to be looked at, at all? Because it's never been part of the dosimetry.

Smith Apisarnthanarax: Right. That is correct. The neutron contamination is really nonexistent for pencil beam.

Mika Sinanan: You're talking about neutrons caused by the protons?

Sheila Rege: Correct.

Andrea Skelly: By the way, in the full report, there are tables for each of the cancers that describe whether it was . . . if the authors gave us that information whether it was pencil beam, scatter, or whatever, but we tried to capture that. It wasn't always well reported.

OK. So, moving on, then, you're all familiar with the key questions. So, I won't go over them, other than to say that the focus of this report is on the comparative effectiveness of proton beam versus other radiation or other forms of cancer treatment. That includes cost-effectiveness studies, as well.

In terms of the populations, we didn't exclude any tumors, any that came our way through any of the literature were included. If the other criteria were met, proton beam therapy, of course, was the intervention of interest, and again, comparators included any other radiation therapy alternatives or other treatment alternatives specific to each type of cancer being treated. The primary outcomes were improvement in overall survival, progression free survival, local control. The others were not provided information. Adverse events directly attributed to proton beam, again looking primarily at different comparative toxicities and cost-effectiveness outcomes.

In terms of the inclusion criteria for study design, we focused on the highest quality studies. In other words, those that have the least risk of bias, which included comparative observational studies, which comprised the majority of the studies in this report. Case series were considered, but not extensively, because the focus of the report is on comparative studies and these studies were primarily considered for safety issues. We also did look at safety issues, as well as full economic studies. For publication, full length studies published in English peer-reviewed journals, and studies published subsequent to the 2014 report were the studies that we looked at. We did exclude mean abstracts, white papers, editorials, and letters, as well as model policies, as that as not part of our scope. Furthermore, contrary to what I heard some of the speakers say, the report does not make any recommendations about policy. Nor did it evaluate any related policy issues.

Given that the majority of studies included are observational studies and not randomized control trials, and in some cases, that's logical. A randomized control trial would not be appropriate. We talk about that here in a moment, but it's important to consider, what are the areas for bias in observational studies. Those include selection bias, attrition bias, performance bias, performance bias, detection bias, reporting bias, and confounding. Among them, very important to consider that selection bias had occurred on substantially in the studies that were included. Many of the studies included patients who got proton beam therapy when it was available, but the comparison cohort was a group of individuals who had photon therapy prior to the availability of proton beam therapy, which then leads to a discrepancy on followup, which may impact longterm outcomes. Some of that had been mitigated through some of the analytic pieces for some of the studies, but it is an important thing to consider that that's part of selection bias. Loss to followup is an important consideration, as well. Some studies did count the loss to followup. Some did not. Confounding, by indication, is a very common thing in

observational studies. That occurs when individuals who have maybe more severe disease or a different type of disease preferentially get one treatment over another. Again, sometimes you can't avoid that, but it still needs to be considered. Then, differential referral for treatment also could happen. Attrition bias is another important one to consider. If more patients in one group are lost to followup versus another group, it sets you up for differential efficacy or safety evaluation. Performance bias, we won't get into. Detection bias, again, for many of the hard outcomes, like overall survival, etc., it's not an issue to have blinded assessment. The validated instrument, etc., is very important. The culpability in length of followup, I already mentioned, for each group. Confounding is also an important issue. All the studies that were included that were observational did have discrepancies in baseline characteristics, and most of them did control [inaudible], and we'll talk about that in a moment, but all of these may, in fact, be observation of an effect or lack of observation of an effect. Some are difficult to control in retrospective study. They may be able to be controlled in a prospective study.

These are criteria that relates to those potential biases and observational studies, but also RCT's can be bias, as well. I focused on complete followup, lack of . . . less than 10% difference in followup between groups, and a control for confounding as being the most important in the studies that we evaluated. The criteria that we used based on the Cochran Risk of Bias tool. The individual studies were then put together. The primary outcomes were assessed overall strength of evidence based on the criteria that you're already familiar with. This slide is only one of those. Consistency across studies is another factor. The directness of an outcome, and the precision, level to which there is variability in the effect [inaudible]. Then, report bias/publication bias, which is very difficult to assess. Going back, I want to point out that this is a bit of a departure from some of the reports that we've given to this committee.

Generally, the strength of evidence, the application of the criteria that I just mentioned and the grade process, RCT's are considered initially high strength of evidence and observational studies are initially considered low strength of evidence. However, when randomized control trials are not available, unethical, or not feasible, high quality, and I emphasize high quality, nonrandomized observational studies may provide the best evidence. Certainly, there are many cases that you've heard from the public commenters, but also other cases in medicine. The caveat is, that doesn't make the quality of these studies better. There is still the potential for bias that needs to be considered. What that means, in terms of decision making, is that you need to accept that there is a degrade or uncertainty around the estimates, that the estimates really do reflect the

true estimates, if you were able to do a high-quality randomized control trial. So, nonrandomized observational studies, especially [inaudible] ones, certainly can be well designed to mitigate bias and to control the confounding. So, with those few limitations and those which controlled for bias were initially considered to be at moderate versus low risk of bias. Then, we downgraded based on other factors. So, initially, ideally, we would have liked to have seen studies that control for confounding with at least 80% followup and less than 10% difference between treatment groups. So, the systematic review process, as I mentioned, follows accepted methods for systematic review and studies that were included have already been discussed. We assess each individual study for risk of bias. Then, taking a look at the primary outcomes, adjusted overall strength of bias, which gives us an estimate of the confidence about the true effect being very high, very confident that the true effect is what we're seeing in the literature, moderately confident, limited confidence for low, or insufficient where there's no evidence or no confidence in the effect.

With regard to reconciling to the 2014 report, it was important for us to consider how to evaluate the next health benefits based on their algorithm. So, we also considered some very general things, in terms of evidence quality, the comparators that we used, whether the new evidence was a major change in evidence base, or substantial change in the effect size, or a statistically significant result beyond just a borderline typical significance, and evidence of substantial harm. So, then that health benefit considers clinical benefit and potential harms, as well, of comparators versus proton beam, again, based on the 2014 report. Superior health net benefit was generally applied when there was an increase, especially a large to moderate increase in effect size for effectiveness, and a decrease in harms. Incremental health net benefit was considered when a small health benefit was considered versus the comparators, and that could take a form of a small effectiveness, no difference in effectiveness, and a reduction of harms. Comparable effectiveness, comparable health net benefit was considered where there may be tradeoffs in effectiveness and harm, but overall, things in the benefits were comparable. Things in the harms were comparable. Inferior health net benefit would mean that there is a negative health benefit maybe due to increased harms or if there was insufficient evidence to really determine the net health benefit versus a comparator.

Mika Sinanan:

In the written comments and the comments from our speakers, there has been concern that the process for review may not have adequately captured either the harm or the benefit, or the combination of both. So, you heard my question about, the difference between either the measure

of the benefit or the harm and the magnitude of those two adequately captured by the process we went through. My question to you is, do you believe that with the considerations that you outlined on your SOE slide, number 18, and the comments that you made, as you adjusted for the nature of the evidence that is available for this kind of technology, that we appropriately accounted for that concern? Or, that's one possibility. Or the other possibility, it seems to me, is that the criteria that you were handed as part of this review process, as part of the standard for this committee's reviews, required that you do this, but in fact there are built in biases or limitations to that review process that may have excluded or changed the outcome of your summary?

Andrea Skelly: We could spend a lot of time talking about that. First of all, let me say that the process that we use for systematic review follows guidelines for quality systematic reviews put out by the Agency of Healthcare Research and Quality, the Institute of Medicine, PCORI, and others. The intent is to provide an objective evaluation of what should be included and what should be excluded based on predefined criteria, which was specified in the documents at the time of the key question posting. We did consider public comments and the extent to which they followed what the intent that we were given for this particular report. So, certainly, we have taken the pains that we can to ensure that we have been as objective, as possible. So, that's one part to the answer. The other part to the answer is that, during public comment, both during key questions, as well as the draft report, numerous documents for model policy and some clinical guidelines were put forth in the public comment. Again, our role was not to evaluate policy. So, what we did is, we took over 1400 citations from those documents to assure that they did or did not meet our inclusion/exclusion criteria. We also took any that were cited by the public commenters and compared them to our inclusion/exclusion criteria. The exclusion criteria are, again, listed in the documents, in the table of inclusion/exclusion criteria. So, we feel like we have taken . . . we've done our due diligence to assure, to the best of our ability, that we have been objective in considering the literature that is important to the field, but also following standardized methods for including those studies. Does that answer your question?

Mika Sinanan: So, thank you. That's helpful. I wanted to make sure that you've had a chance to sort of outline your perspective on that, because at the end of the day, one of the key questions, it seems to me, is expert opinion may lead us to a different conclusion or recommendation than the review of the data does. Then, the question is, is the expert opinion relying on information that is not captured in the studies, because of the exclusionary criteria? Was never studied? Or is there bias in the expert opinion that is

leading them to come to a different conclusion than the data. That's one of the . . . that's kind of a key question that we will have to deal with, but part of it was, do you believe that you had, to the extent possible, mitigated the effects of the limitations of the data by the review process. I'm taking your answer to be, as much as you could, you did.

Andrea Skelly: Yes. Again . . .

Gregory Brown: If I may intervene here so that we can move forward, but I would remind the committee that I didn't hear the evidence in your statements. I heard data, and I heard opinion, neither of which are evidence. So, that's why we do have the report. So, if we can keep going with the report, the key is the evidence. So, there is certainly plenty of opinion in the room, and there is data, but data in and of itself is meaningless. It's once it's processed and information to become evidence, which is what you determine, based on your review process. Is that correct?

Andrea Skelly: Yes. Thank you. Again, to the other part of your question, yes. We did take into account sort of the unique nature of the available data and uniqueness of some of the patient populations by evaluating it in this way.

Smith Apisarnthanarax: So, you mentioned that you followed standard criteria of what to include or exclude with other various agencies that you mentioned. However, there are nuances that radiation oncology . . . some of those criteria may not apply. So, the very core of what we do is dosimetric comparison and trying to determine, what's the amount of radiation exposure to the different organs and that nuance is not applicable to any other field of medicine. So, I'm wondering, the decision to exclude those kinds of studies that are very specific to radiation oncology and you can apply it to any other field of medicine, was that taken to account?

Gregory Brown: So, I'll make a comment. Again, if you'd like to comment, too. So, there are various ways to grade evidence. [inaudible] we use has five levels of evidence and expert opinion is level five evidence. I have my Ph.D. in engineering. I do a lot of biomechanics work. Unfortunately, basic science is also level five evidence. So, from my perspective, dosimetry is basic science. I believe in physics, but that doesn't mean that the physics translates into a clinically important benefit. Just the fact that you can do the physics doesn't show that it's a superior treatment. So, again, that's why we look at evidence, not basic science. So, if we can proceed.

Andrea Skelly: OK. Thank you for that perspective. Our focus is on clinical outcomes. There were three dosimetric studies included for prostate that are not part of the overall strength of evidence. They were included because they did

impart information about clinical information versus modeling or doses, which may or may not have a clinical effect reported.

OK. So, moving on. We had talked about the confidence made back in the strength of evidence ratings. We've looked at how we've evaluated things. So, we had total citations of over 2000 citations that we reviewed. Again, we had over 1400 citations from public comments for most all of the ASTRO guidelines and the model polies that were submitted of those after decreased after getting rid of duplicates and looking at our inclusion criteria and exclusion criteria, we evaluated 408 of those for potential inclusion. You can see them. We have over 215 studies included in this particular report. Most of them are case series. They are summarized extensively in your appendices. Again, our focus is going to be on the comparative studies that we identify.

Compared to the 2014 report, the 2014 report had two randomized control trials, 38 comparative studies most retrospective, and many of them were indirect noncontemporaneous case series where they took cases from one institution and compared them to another institution, which induces a bias and potential evaluation of effects. There are 245 case series approaching economic studies, and 4 contextual studies. Again, those were just some of the few studies that were included for context in the previous report. This report includes two case series, one quasi randomized control trial, 49 comparative studies with most retrospective, and over 150 case series cost-effectiveness studies, and again the 4 contextual studies done. The retrospective comparison study limitations, again, may impact results, because the treatment is based on historical changes and radiation therapy methods, again, have differential followup in terms of length of followup. They could have had differential loss to followup, as well. There is a big potential for treatment selection by confounding by indication, and unfortunately, the completeness of followup and loss to followup were poorly reported or could not be determined from the way that the studies were reported. There were substantial differences in some studies in baseline characteristics, and there is a potential even though they control for confounding or residual confounding. I say this, because all of those factors can go into seeing whatever is statistically significant effect is or didn't materialize.

In terms of the organization of the results, we will go by, again, focusing on the comparative studies. The key questions were based on proton beam use for curative intent. Key question two, for salvage or recurrent disease. Then, comparative harms and safety, differential effectiveness. There were no studies for differential effectiveness of safety, and, where available, we report on comparative effectiveness studies for cost-

effectiveness. We'll start with the pediatric tumors and go through all five questions. Then, we'll go to the adult tumors. We'll go basically in alphabetical order based on the comparator studies. Some of the case series are extensive, and they are found in Appendix F starting on page 26, and they do include the primary outcomes of interest, such as overall survival, progression free survival, etc. There have also been special appendices for the safety issues. If you really want the gory details, the separate appendix on data abstraction incorporates all of the gory details for all of the case series, as well as the comparative studies.

If we take a look at the evidence base for the new report and the old report, the old report only reported on one comparative study. It was a very poor quality study that looked at secondary malignancies in pediatric patients who had been irradiated at a young age, and they felt that the evidence was really not very good. In 2019, we have a substantial increase in the number of comparative studies. There were eight comparative studies in the pediatric brain, one retrospective study in head and neck cancers, and one of salvage therapy for ocular. So, there were quite a few additional studies to evaluate, but most of them were in the pediatric brain. If we take a look at key question one for curative intent and pediatric brain tumors, overall survival was consistently not statistically significant at any time periods drawn across three retrospective studies and one prospective study. Some differences, however, make it clinically significant, and I would point out that statistical significance and clinical significance are not necessarily one in the same. An additional retrospective study also verified that there were no statistical differences between proton beam or conventional radiation therapy. The strength of evidence was low for both of these instances. Again, case series can be found in Appendix F.

With regard to progression free survival, either versus IMRT or 3D conformational, proton beam therapy did tend to have better progression free survival, but it was not significant for the study that looked at ependymoma at 3 years nor at 6 years. It was not reported, the statistical significance was not reported at 6 years, but it was not statistically significant for medulloblastoma. There was a lower recurrence rate with proton beam therapy in one study by Sato. These related mortality was substantially less for proton beam therapy versus IMRT, but the strength of evidence was low.

If we take a look at endocrine-related abnormalities, which are a concern in pediatric patients, they tended to be less with proton beam versus 3DRT or IMRT, but again, statistical significance was not uniformly reached. I would point out that the patients in Eaton and Bielamowicz had

conjunctive chemotherapy, which may or may not impact the process [inaudible] that we see. The strength of evidence was low. The role for sample size, selection bias, and other things may not be clear. Eaton did prospectively enroll the proton beam therapy group. The others were all retrospective.

Seth Schwartz: Do you know what the duration of followup was on those studies?

Andrea Skelly: We can look that up. These were . . . they often do not report for the toxicities what the duration of followup was, specifically for those. Where it was provided, we did try to categorize it by acute versus late, but we can certainly look up any of that that you need.

With regard to case series, again, looking at safety, I'm not going to give you a lot of information about this other than to say, these are the ranges that were found in case series, some of which are consistent with what we recorded from other studies, others of which are not. Again, a number of the patients in some groups had preradiation chemotherapy, and again, the problem with case series is that we don't know compared to what? What is the logical comparator here. So, we don't know whether this represents a better outcome versus another type of radiation therapy, or another type of cancer treatment.

Taking a look at the continued safety or other toxicities, both acute and late toxicities, again, tended to be similar or less with proton beam therapy versus with 3DRT or the IMRT, but statistical significance, again, was not uniformly reached. Again, clinical significance may be needs to be considered. I would point out that the study by Song only included 13 people who got proton therapy. The problem with small sample sizes is that it exaggerates the percentage of individuals getting a specific outcome. So, that's an important feature to keep in mind.

If we take a look at case series again . . .

Sheila Rege: Sorry. Could you go back to that. Did you include the study by was it Kahalley in any of those where there was a longitudinal looking at the endocrine and the neurocognitive over six years?

Andrea Skelly: There is a slide subsequently that talks about the neurocognitive. Yes. So, here we go. Case series, again, in terms of white matter lesions, which could be an important toxicity to consider, we have a study that looked at 171 individuals. Grade 3 white matter lesions were less than 1%. Again, you can see radiation necrosis, radiation injury to the CNS or brain stem, vasculopathy, vascular injury, and hearing loss. You can see the ranges

that were reported in the case series. Most of them tended to be fairly low. Again, we don't have the opportunity to compare it to an alternative form of treatment. Again, tables 60 through 68 provide you a lot more detail summarizing the case series safety information.

So, here's Kahalley. There are two studies by Kahalley. Kahalley 2016 was a retrospective cohort, and it looked at proton beam versus photons. They did not give us means. They only gave us adjusted beta [inaudible], but there were no statistically significant differences, but there were no statistically significant differences when all patients were considered, or when patients who got spinal irradiation or focal radiation therapy. The strength of evidence was, however, low, but there was no difference between those two treatments. More recent Kahalley looked at various brain tumors. It was prospective. It's an ongoing cohort. When they compared proton beam therapy versus surgery, there were no statistical differences in the full-scale intelligence quotient or any of the subscales. The scores actually remained stable for both groups over the time period of followup. When craniospinal irradiation was compared to surgery, however, there was a difference between the proton beam therapy, and it was associated in a decline in the FSIQ, as well as some subscales versus surgery, but the authors do not describe clinical significance or any sort of threshold for those changes. Again, they don't give us means. They give us basically data [inaudible], which are very difficult for even statisticians to put a lot of meaning in, to some extent. Again, the strength of evidence was low.

With regard to cost-effectiveness, there were two cost-effectiveness studies dealing with pediatric brain tumors. One was in Japan, was construed to be a poor quality, and they felt, based on their analysis, that in a threshold of \$46,729/QALY, in their currency, proton beam therapy was more effective than conventional x-ray therapy. I would point out, however, they really didn't adequately describe the cost of proton beam therapy. The clinical outcomes are from cases series data, even though they're making a comparison to conventional radiation therapy, and that information was derived from a small case series of eight patients. They didn't consider longterm outcomes related to motor, physical, or intellectual challenges, or longterm healthcare challenges or costs in their analyses. The study may not be applicable to the U.S. situation. In addition, the utilities were based on hearing aid use without specific information about a postradiation population of children. Utilities derived were from adult populations and may not be applicable to the study population that we are studying here. The incremental cost-effectiveness ratio varied by whatever utility they used.

If we take a look at the other cost-effectiveness study, which was in the U.S., it is considered to be of poor quality. This is in patients with CNS tumors of variety. They used hypothetical cohorts used exposed at either age 4 or age 12. They don't really talk about the timing or use of proton beam therapy or [inaudible] therapy versus conventional x-ray therapy. They basically look at the dosimetry proton/photon dose combinations. Many of them did suggest that at lower doses of proton beam therapy, there would be cost-effectiveness or cost savings at a willingness to pay of \$50,000/QALY, but it was not effective at the highest proton beam therapy doses versus photon radiation therapy. They concluded that the proton beam therapy may be cost effective when the radiation dose to the hypothalamus was spared, but it may not be cost-effective when a tumor is involved or directly adjacent to a hypothalamus and the radiation doses are high. Again, that model is not well specified. There are limited parameters in the model, and there are no longterm toxicities, such as auditory or cognitive effects that were included in the model other than a growth hormone deficiency. I forgot to say that that was, what they were modeling. Again, the data are from case series with no longterm comparative data that were available to evaluate their assumptions of a quality and outcomes between proton beam and photons. Again, the proton beam modeling operational costs do not appear to be well detailed. Sensitivity analyses were very limited. Again, the utilities were from adult studies and assumes the costs of therapy for adults is comparable to that of children. So, there are a number of limitations to be considered.

We're gonna shift gears to talk about the only comparative study that looked at head and neck tumors. There was a small retrospective study of salivary gland cancer. There were 24 patients, and the study suggests that there was . . . that mucositis was less common following adjuvant proton beam therapy, but there were similarities in the other toxicities. However, because of the size and potential for bias for this study, it was considered to be insufficient evidence.

Ocular tumors, there was one study, again, a very small study that reported primarily on eyes, not numbers of patients involved. It was considered to be at serious risk of bias. The bottom line was is that the enucleation presurvival was lower with proton beam therapy plus the small sample size may have precluded detection of a clinically or statistically important difference. Then, for the other toxicities, although they were more common with proton beam therapy, the difference was not statistically significant, but again, the evidence was very limited, and it's based on number of eyes, not numbers of patients.

If we take a look at the summary, the proton beam therapy report from 2014 had only one comparative cohort study. That's what CC stands for. There were 41 case series and 3 economic studies. The updated report now has ten comparative cohort studies, and those were then focused, like I said, mostly on the brain. The previous report did not break their assessment of by cancer types and pediatric cancers. We had the luxury of doing this to some extent. Consistent with the previous report, it appears that the benefits, in terms of overall survival and progression free survival, it appears to be comparable, but there is evidence that harms were less common in proton beam therapy, though not statistically significant in some cases, but it was felt that there was evidence for incremental benefit, net health benefit based on those new studies. For head and neck cancer, again, because of the poor quality of the studies, we felt that the evidence was insufficient to draw conclusions. The rest had case series, and those were considered insufficient.

In summary, the pediatric findings, we felt that there was incremental net health benefit of proton beam versus other treatments. Again, mostly, it was proton therapy for brain tumors, based on six retrospective and two prospective cohort studies. There was no comparative evidence for the tumors you see listed here, and no evidence met the inclusion criteria for other pediatric conditions. There is insufficient evidence to determine comparative net health benefit for the head and neck and the salivary gland tumor is the only example that we have, and salvage treatment for the ocular tumors, which was retinoblastoma. Again, this may or may not apply to other tumors. The two economic studies were poor quality cost utility analysis. Conclusions regarding cost-effectiveness are a bit challenging given that the data sources were case series, and that they used utilities from other patient populations. The model specifications were limited and there were limited sensitivity analyses.

Comparing, again, to the 2014 report, we now have comparative studies where they did not previously, and for pediatric brain tumors, the low strength of evidence suggests that there was incremental benefit of proton beam therapy. The benefits were comparable, the harms were lower. For other pediatric tumors, basically we do not have sufficient evidence to draw any form of conclusions. For key question four, which is the differential effectiveness, there were no data available. Are we ready to go on to adult tumors?

Gregory Brown: Questions? What I'm hearing you ask is it easier to kind of ask questions separately than all at once at the end and?

Sheila Rege: I would like separately.

Gregory Brown: OK. Alright. So, should we kind of ask the questions now then, and then we'll do . . . then we'll go on to adults? Any questions regarding pediatrics from the committee?

Sheila Rege: I'd like to, oh, I'm sorry. I'd like to hear from the expert on pediatrics if . . . just your thoughts.

Smith Apisarnthanarax: So, I'm not an expert in pediatric cancers. So, it's hard for me to comment on every single study that has been done here, but, uh, other than the fact that, you know, there are other metrics that are not taken into account, but I realize that you're evaluating what was available that has been published.

Sheila Rege: Thank you.

Mika Sinanan: When I talk to patients, myself, about the options for cancer treatment, and I go through surgery and chemotherapy, radiation, and no treatment. Those are the four different options, or combinations of them, I say, not as a radiation oncologist, I say we can kill, 'we', the big 'we', can kill every cancer with radiation. We just have to turn it on and leave the room, and we will kill the cancer. The question is whether we kill you in addition to the cancer. It's very clear to them what the difference is. So, when we talk about the differential sensitivity of tumors to radiation, is it really about the ability to deliver enough radiation and not kill the surrounding tissue, not cause unacceptable harm to the surrounding tissue. Is that always the situation, or almost always the situation?

Smith Apisarnthanarax: So, there are cases where you are not able to deliver what you need to, to the tumor, because you're exceeding constraints on your surrounding organs, and then there's other scenarios where you are able to deliver adequate but with protons you're able to better spare normal tissues. It depends on the case. It's a case by case what the intent and the benefit is for these protons. Does that answer your question?

Mika Sinanan: So, my, sort of. My understanding is, when we talk about a radioresistant tumor, it's not that it is resistant to radiation at any dose. It's that, at the dosage you could feasibly deliver within acceptable toxicity to the surrounding tissues, you can't deliver that dose. That's a radioresistant tumor. Is that an accurate statement?

Smith Apisarnthanarax: So, there's an always an inherent radioresistance. Whether you can overcome that radioresistance is tied to whether you're able to achieve in relation to exposure to the normal organs.

Mika Sinanan: So, I would infer from that, that this issue, because a lot of this comparison is survival and effectiveness of the direct treatment in, as you pointed out earlier, one of the key questions in radiation oncology was kind of unique . . . and actually, it's not that unique, because it's the same with surgery in many ways is, what can we do while sparing vital structures around it? 'Cuz we're faced with that all the time. Right? Can we take out something and not create such a disability or a lethal risk to the patient by doing that, and it's the same question you're facing. So, it's actually a very similar type of question from both standpoints, in which case, the consideration of the surrounding tissue toxicity becomes really a critical decision point. Is that right? Yes? OK.

Seth Schwartz: Just back to my earlier question about the duration of followup that we have. I think we talked about early and late, and I think as this discussion has gone on, it seems that the late consequences are one of the things that may be inadequately captured in some of these studies. So, I guess I would just ask if, number one, you have any comment regarding how well the studies that we looked at capture the potential for late side effects, or late toxicities. Secondarily, what we actually did look at.

Andrea Skelly: So, in terms of length of followup, we can refer to the study table one in the report. That gives us the general length of followup for these. For the survival, we delineated whatever there is, but I know you're interested primarily in the toxicities. If Erika or Shelby can tell us what table 1 is for the pediatric study . . . what page that is on the full report and maybe help us understand for the toxicities for the pediatric studies. There is some . . . . 30 days, less than 30 days was usually considered acute. Over that was considered late. Here we go. We do have some information here about the neurocognitive effects. Let me go back a little bit further, though. So, for some of these here for the other toxicities, Song did not provide us information about that, other than that they were acute. For the other toxicities listed here, for Bishop, Paulino, Sato, we'll have to look those up. I think those were later toxicities. Again, I don't know the specific finding. If . . . I'm sorry what? Pages 76 and 77 have the detail of the studies. Thank you. It has the followup. Thank you, so much. For the case series, you can see that someone did a cumulative incidence at three, five, and seven years. Someone did a probability of [inaudible] deficiency over a ten-year period. It varies. So, if we go back to the first slide of toxicities, for the endocrine toxicities, we have studies by Bielamowicz, Eaton, and Bishop. I don't know what the page says. I don't have the report for the followup for those particular studies. So, on page 76 of the full report, the length of followup was, again, because of the differences in the way the cohorts were pooled together for Bishop was 33 months for proton beam

group versus 106 months for the proton group for proton beam. In Eaton, it was 74 months versus 84 months for the proton group. For Sato, 31 months versus 58 months. So, there is differential length of followup overall across those studies.

Smith Apisarnthanarax: I didn't see a slide on any studies about secondary malignancies that might be radiation induced.

Andrea Skelly: Based on the studies that we had available to us, that was not reported. There was a previous study in the old report that we reported on secondary malignancies, but it was unclear why they were excluding some of the secondary malignancies, and it was included in the previous report, but our . . . what we have here did not report on that.

Smith Apisarnthanarax: You mean in the last five years, you mean?

Andrea Skelly: Yeah. In the last five years literature. That's an important point, again, when considering the length of followup for some of these studies. It may not have been long enough to detect that. Again, differential length of followup between the photon and proton groups, and the development of those secondary cancers is something that might need to be considered, as well. So, because I don't know whether that answers your question, it's kind of hard to go study by study. Some of the toxicities here, again, we'd have to go by the general what was reported for the toxicities here. Again, these are not well delineated here for Kahalley for the cognitive, 34 months versus 64 months and 33 versus 37 months.

Seth Schwartz: That's helpful. I appreciate that.

Andrea Skelly: OK. Thank you.

Mika Sinanan: So, followup question, Jim. Would the toxicity surrounding tissues, say the endocrine toxicities be cumulative over time and increasing over time for decades? Or does it flatten? Does the curve flatten after two years, five years, ten years? Do we know for radiation in general? I'm not talking about just pediatrics and not just proton beam.

Smith Apisarnthanarax: So, I don't know if I know the exact question to that. It's certainly considered a late toxicity whether there's a certain five, ten year peak. Actually, I'm not clear on that.

Mika Sinanan: So, let me ask it this way. If you irradiate somebody's thyroid, as a part of laryngeal cancer, if the patient doesn't have hypothyroidism in five years, is it likely that they are not gonna have hypothyroidism at ten years or

fifteen years? Or do we not know? In other words, does the toxicity from reduced function occur and then the effect stops? Or does it continue to rise?

Smith Apisarnthanarax: I don't know if I can quote data, but my estimate would be that there is always gonna be a lifelong risk of developing late toxicities, whether it's endocrine or otherwise.

Mika Sinanan: So, you think it's accumulative? It progressively increases over time, though the rate may not be the same.

Smith Apisarnthanarax: Right. I'm not sure exactly on that on the peak incidence and all that, but, in general, any late toxicity is accumulative, that it can . . .

Mika Sinanan: We think about that for bowel toxicity. Do you, Sheila, have you thought about that question?

Sheila Rege: Maybe for head and neck cancers, hypothyroidism. It's a late effect. It doesn't show right away. So, does that answer your question?

Mika Sinanan: Oh, so the followup study that Seth was asking about had a five to six year followup. That's a late interval. So, does that accurately represent the toxicity? Or is that just an interim measure? And is it going to continue to rise, as the child gets older?

Sheila Rege: I think that yes. We would say it possibly will continue to rise. The issue is going to be, we have a lot of longterm data for photons. So, we . . .

Mika Sinanan: And what's that suggest?

Sheila Rege: It's not as high and not as worrisome as you worry about as a surgeon, because most surgeons, when they send a patient to radiation, that's the fear is that radiation's longterm toxicity will be quite high, especially bowel and stuff, but we know that with photon radiation, we've got several years of toxicity, and depending on the organ, it's not as high. Our hope is that protons, with its shorter or tighter distribution radiation, would be less.

Mika Sinanan: Hope, but not evidence?

Sheila Rege: But no evidence.

Smith Apisarnthanarax: But I think that speaks for the followup. I think, you know, depending on the followup of the study . . .

Sheila Rege: I should say 20 years evidence. I'm talking, 10, 20 years. Not photons or protons.

Smith Apisarnthanarax: . . . so, if you're looking at it too short, you're not capture the patient's that are gonna develop later than that. So, it is accumulative effect, and it really never goes away, especially for secondary cancers that risk continuous time, 15, 20, 30 years later. So, some of these studies may not capture the whole gamut of risk.

Andrea Skelly: Moving on to adult tumors then. We've been focusing on the comparator studies. You see that most of the comparator studies were again for curative intent. There were only three that were other than for curative intent. Again, we have a greater number of comparative studies, which is all we're really showing here. And we had several economic studies, as well, to be considered. There were 37 total comparative studies, again, 34 of which were for curative intent. In terms of adult tumors, again, we focused on new comparative studies reporting primary outcomes, overall survival, and progression-free survival. All but three of the studies, again, were retrospective cohorts, and they were moderately high risk of bias. Unfortunately, not all of these studies reported on the primary outcomes. So, that's why those of you who like to count studies may be disappointed that some of the studies that we have on the slides are not the same as the counts that you see in some of these slides, because not everybody reported on every outcome.

Here, we have two different types of tumors in the adult brain. These were derived from comparative studies that show very different results. Large comparative cohort, which is a database study, the adjusted hazard ratio suggests that proton beam was favored in terms of overall survival at five years. However, if we look at the patient population, 136 patients who had high-grade glioblastoma in a retrospective cohort study, we can see that there were no statistically significant differences between proton beam boosts with protons versus photons alone. The percentage of probability were somewhat less with photon with proton beam boost versus protons alone, which are in the light blue, but again, this was fixed information there. We looked at the progression free survival. Certainly proton beam plus photon appears to be better, but again, statistical significance wasn't reached. Clinical significance needed to be considered.

Looking at adult brain, again, the other comparative study that we have was on [inaudible] therapy, a very small retrospective cohort looking at CNS involvement of lymphoma or leukemia prior to stem cell transplant would be considered to be insufficient evidence because of the risk of bias, as well as the study size, but there were no differences between the groups

at six months and overall survival, but they did not really report on statistical testing. There were no statistical differences in relapse for the CNS tumors. The sample sizes may have precluded evaluation of differences between treatments.

Taking a look at safety, toxicities in the adult brain tumors, acute toxicities defined as less than three months, and radiation necrosis and change in symptomatology reached that there were no differences between groups. It is unclear if some of the differences could be clinically important, but again, with a sample size of 132 patients, rare outcomes are not possible probably to detect, and it may have played a role that there were no statistically significant findings either in grade 2 or grade 3 toxicities, or in those other toxicities, neurocognitive deficits, sensorimotor deficits, and new or worsening in any of those for seizures, but the strength of evidence was considered to be low.

Looking again at a small case series in the same small case series, a few toxicities during craniospinal irradiation, we find that again proton beam did result in a lower frequency of mucositis of any grade, but no differences were seen over the acute term or late term between the groups. Again, sample size likely plays a role in this, and evidence was considered to be insufficient. One late toxicity was reported, and that was severe CNS neurotoxicity, which was 7% in the proton beam group and 14% in the proton group, but again, we felt that it was insufficient.

If you take a look at the range of the various toxicities reported, again, focusing on grade 3 or higher toxicities, these are the ranges that are across the case series that were summarized for any acute grade 3, the range was from zero to 17.4%. The length of followup, median length of followup was 20 months to 56 months, 57 months, and you can see that some of the ranges are related also to the other toxicities here. Five-year toxicity free survival in one moderate sized case series up to 56 months was about 89.1%. Again, we don't have a comparator. Radiation necrosis 24%, brain necrosis 32.1%, proton related neurotoxicity grade 2 or higher 44%, and radiation therapy related mortality 1%, but again, sample sizes played probably a role, and without a comparator, it's hard to know whether this represents effects specific to proton beams, or if it's comparable or different to other treatment options.

Looking again now at a summary of the brain tumors, we do have a little bit of a difference in what was defined from the 2014 report. We have five comparative studies, only three of which are represented here, because again, not all of the studies reported on the primary outcomes. The 2014 report suggested that the benefits were comparable, but there were

decreased harms. The 2019 report, it appears to depend on the type of comparator that's used for proton beam versus photon. It was felt based on the evidence summarized that there may be an increase in benefit when adult brain tumors were evaluated, but we didn't have adequate information on harms. So, that benefit is unclear, because of lack of reporting of harms for [inaudible]. Looking at proton beam boost with photon versus photon alone the, matter of fact, was considered to be comparable. Again, because of the risk of bias and small sample sizes for salvage treatment, was felt to be insufficient. It's important to note that between the 2014 and 2019 reports, different tumors were studied. Also, there were very different proton beam protocols and comparators, and they are listed here for your convenience. So, that may lead to some differences in conclusions between the two reports, and the studies from the 2019 report were larger, and they did include one large database study, which did not report harms. That was for the proton beam versus photon. So, the evidence for proton beam versus photon for CNS metastases was, again, insufficient.

If we take a look now at breast cancer, a newly published study, again a retrospective database study, reported five year survival among patients who had breast cancer and received proton beam therapy or versus photon or electron boost therapy. The adjusted probability suggests that proton beam had higher overall survival. Their adjusted hazard ratios, however, seemed to be not statistically significant, and there were no differences between proton beam therapy versus photon electron boost therapy for the probability of overall survival at five years; however, the strength of evidence was considered low, and because the study did not involve evaluation of harms, we cannot provide information on comparability of harms. There were no studies of salvage or comparative safety for the breast cancer group. All the rest were case series.

Across case series, there is the frequency of acute events, grade 2 or better, grade 3 or worse, and late grade 2 or worse studies, but there is limited information, again, because we don't have comparisons.

There was a cost-effectiveness study, which was reasonably well done. It was in women with breast cancer, and they looked at cohorts of women at 40, 50, or 60 years old who did or did not have cardiac risk factors associated with the . . . and again, these are modeling of hypothetical cohorts. The finding of proton beam therapy and photons was not delineated. The cost-effectiveness ratio did vary by dose and the presence or absence of cardiac risk factors. The range for cost-effectiveness was quite wide, as you see in this slide here. It ranged from being cost-effective at \$50,000/QALY to over \$890,000/QALY, depending on the dose and

depending on the age cohort, and the number of risk factors. The authors included that for women who do not have cardiac risk factors, proton beam therapy was not cost-effective, and the willingness to pay are at \$50,000/QALY, that it may be more cost-effective in women who have at least one cardiac risk factor or for younger patients. The modeling for their Markov model transition probability was not clear, and the sensitivity analysis shows a very wide variety of ICERS depending on the assumptions that are evaluated. They did not look at outcomes other than coronary artery disease, coronary heart disease, death was not modeled, utilities were not detailed. They used the lifetime horizon but do not provide any information on comparative data for making that assessment, and it's not clear that they incorporated all costs for the operation proton beam therapy. I think one of the more important pieces, or as important, is that they used case series on proton beam therapy, and they used a case control study, which was a very good case control study of radiation related risks for ischemic heart disease in women who had received radiation therapy between 1958 and 2001, and one of the concerns is that while that was a very good study, it did not maybe capture more recent advances in radiation therapy.

So, in summary, for adult breast cancer, we do now have a cohort study, which was not available at the time of the previous report, and unfortunately, while the benefits appear to be comparable, there is no information really to decide net benefit based on the fact that harms were not reported.

If we move now to esophageal tumors and look at overall survival, all we had to look at was retrospective cohort studies, and there are two very different studies looking at different patient populations. While the tendency to look across the data at one year, two years, three years, four years, five years, it suggests that proton beam therapy did concur better overall survival. One study did not find that the results were statistically significant, the other did. It may, again, be very difficult to say way. It may in the differences in patient population, differences in the delivery. One of the studies, the Fang study, did use a propensity score matching to try and help even out the differences between the two cohorts. It's unclear to what extent a lot of factors may be involved here in looking at the differences between these two studies. The strength of evidence, however, was low.

In terms of additional studies for esophageal tumors, looking at mortality, we have two very different studies. One is a very small study using definitive chemoradiotherapy. Another is a larger study using trimodal therapy. And we can see that there are no statistical differences in

mortality between proton beam therapy and either x-ray therapy or 3DCRT or IMRT for any of the timeframes indicated here. Again, strength of evidence was considered low.

We looked at the progression free or disease free survival, and you see a pattern that proton beam appears to infer maybe better progression free survival versus IMRT; however, again, studies conflicted whether they were statistically significant or not up to a five-year survival. Strength of evidence, again, was considered low for all.

Regarding distant metastasis and locoregional failure, which was reported in one of the studies. We can see, again, that proton beam therapy appears to confer better control over just the metastases and locoregional failure free survival. If we look at safety, we find a variety of results. They are somewhat conflicting. For some types of toxicities, the results between the two treatment groups are not statistically significant. However, for some of the studies, there is evidence of statistical significance for some types of toxicities represented in the slide here. This [inaudible] report if you need a clearer picture of it. So, there is inconsistency to the extent to which things are statistically significant. Again, there may be some clinical significance associated with this. There does seem to be some tendency toward some of the toxicities to be lower with proton beam therapy.

Here again, we see that there are fewer adverse events or toxicities seen across two retrospective cohorts, but again, not all findings were statistically significant. The clinical significance for some of these differences are unclear. Again, proton beam therapy seems to be confer fewer toxicities overall. Some of them may or may not be different compared to other forms of radiation therapy. In terms of case series, again, all we can do is provide what the range of toxicities were in terms of acute toxicity. Again, using three months as a cutoff, some of these patients may or may not have also received chemotherapy in addition, which can contribute to the effects that you see here.

In terms of adult esophageal tumors then, we have evidence from five new retrospective comparative studies that suggest proton beam therapy may be of incremental benefit to IMRT and other forms of radiation therapy based on better survival outcomes and similar or better safety outcomes. The safety, again, results are mixed for some outcomes and differences may be clinically important. I put the box for incremental net benefit in a little bit different color to say that it's kind of difficult to judge to what extent the lack of statistical significance, and the clinical significance across very different types of toxicities might be put into context.

Mika Sinanan: So, I have a question about that. So, earlier we said that the radiation effect between photons and protons was similar. Or at least to the extent that we know that, with some degree of uncertainty, is . . . as we look at this and look at all the graphics that show an improved local control, reduced metastases, overall survival, is it because . . . do you infer this from a . . . from your expertise, Jim, to be evidence that you were able to deliver more of the total energy delivered to the tumor? Is it that you were able to turn to actually give more, because the surrounding tissue toxicity was lower, because of the targeting? Or of the total dose that was given, you gave the same dose to photons versus protons, but more of it actually ended up in the tumor and therefore, had more of an effect? How do you think about that? I mean, why is there a difference between these two?

Smith Apisarnthanarax: I think this is where some clinical context is needed, because you can't lump all esophageal cancers into just one guideline or one recommendation, because it depends on what the intent is. So, for definitive chemoradiation for esophageal cancer, the intent is different than a patient that is going to be planned for trimodality treatment, which means preoperative chemoradiation followed by surgery. Right? So, in the definitive setting, it likely is about how much radiation dose can you give? Because the patient is not going to get surgery, so you need to be able to control the tumor. So, really, it's about dose escalation. In the preoperative setting, it's really about minimizing toxicity so that the patients don't die after an esophagectomy. So, it's well known that a trauma . . . to any surgeon, trauma to the heart and lungs before or after surgery is a nasty thing. So, the rationale behind that setting is very different. So, that is why when you look at the data, you can't just lump all studies into just overall study, one recommendation for all esophageal cancers. So, for example, the one study that kind of showed . . . I can speak pretty well about this, because I do treat esophageal cancers, the rationale for preoperative chemoradiation where the Lin study from [inaudible] showed that there was a reduction in pulmonary events. The theory is that there's a substantial reduction in cardiac dose, and lung dose, as well, which resulted in decrease in pulmonary events. So, I think that's where the recommendation that there was an incremental benefit in the preoperative setting. So, I think that has to be on which the . . . in terms of the intent of the radiation. I think for the definitive setting, there's not a lot of data. There's that one study, but there are emerging studies from the definitive setting that it's thought that it could also benefit in those patients, because as you're dose escalating, you're reducing cardiac dose, which potentially could improve survival, because you're reducing leukopenia, which is, again, a theoretical benefit, but there is emerging

data that is coming up. So, again, I think you just have to put things into clinical context about what you're being recommended.

Mika Sinanan: And these studies combine both the preoperative, the neoadjuvant type of approach, plus definitive treatment?

Smith Apisarntharax: Which studies are you referring to?

Mika Sinanan: Well, your point about that is that, is, did these studies combine those two, or?

Smith Apisarntharax: No. Each study looks at different things, but it seems like the recommendation, you're just making a recommendation just for all esophageal cancers. Right? So, I think if, if one is gonna make a recommendation, it should be with specifically what kinds of esophageal cancer [inaudible]?

Mika Sinanan: Do you think the performance of protons are different between those two categories, the neoadjuvant versus the definitive treatment?

Smith Apisarntharax: I think it's all still unclear.

Sheila Rege: Jim, the Lin study was a retrospective study. That's what you're referring to. Right? OK.

Smith Apisarntharax: We don't have any randomized or prospective studies that are published in esophageal cancer for protons.

Andrea Skelly: [inaudible], trying to do a [inaudible] review, oh, I think in the 2014 report. You're right. We lose the granularity by specific tumor type.

OK. So, moving on then to GI tumors. There was only one tumor, pancreatic tumor, very small patient population. Basically, because of again risk of bias and a small sample size, the strength of evidence was considered insufficient. We did note there were no differences between proton beam therapy and the alternative treatment, but again, some of these may be more clinically important differences. Again, sample sizes really preclude us from making any definitive conclusions about either benefit or toxicities for pancreatic cancer. That was the only type of cancer that had comparative studies.

If we take a look then at head and neck studies, we separated out the non skull-based studies and from the skull-based studies. The strength of evidence was low for primary oropharyngeal and nasopharyngeal cancers,

but was insufficient for salivary cancers, whether they were primary or metastatic, because those were mixed in the studies that we had available to us. If we look at overall survival, we see that overall survival was actually slightly less with the proton beam therapy, and that was from a separate study. There were two studies that provided us with overall survival and three-year survival. One is salivary gland cancer, and one in oropharyngeal cancer as a primary. It looks like in oropharyngeal cancer, proton beam appears to have conferred some benefit. Again, it was not statistically significant, whereas in the salivary gland tumor, it didn't appear to be. They were similar at three years in the oropharyngeal cancer. There was a study of overall mortality, a very small cohort study, looked at primary nasopharyngeal cancer and proton beam all-cause mortality was different in terms of percentage, but there was only one patient in each group had it. So, another example of where a small sample size give you a misleading percentage of patients to compare. If we look at locoregional and distal control, again, we see that there are some differences between proton beam and the comparator. However, none of them were statistically significant. Again, the small nasopharyngeal cancer by Holliday, there were no local failures in proton beam, but 5%. Again, we're dealing with very small numbers for that study.

If we go then to the head and neck safety, the toxicities for non-skull based tumors, again, we see that in terms of acute toxicity, those events, there were no significant differences if you focus on the grade 3 or more severe toxicities for proton beam versus IMRT, and that was across three studies. There are some instances, however, for a study by Romesser where there was statistically significant differences for specific toxicities related to proton beam. Again, generally, the trend was for fewer toxicities for proton beam; however, dermatitis grade 2 or more severe was more prevalent in patients with proton beam therapy. The strength of evidence, again, was considered low. If we look at late toxicities, there were no statistical differences between proton beam and IMRT with the exception of a composite outcome looking at gastrostomy tubes plus weight loss. Looking at the data, it appears to be that neither one of them were statistically significant alone, but when you put them together, they resulted in a statistically significant difference between the two of them, and the others were not statistically significant, again, looking at the adverse events across the studies we have available.

Looking at gastrostomy tube dependence, in the study by Blanchard, which was oropharyngeal cancer, as a primary, it shows that proton beam, again, had maybe less dependence at 3 months and at 12 months. Again, statistical significance wasn't achieved. If we looked at some of the other studies, we really have very little data that were reported. The study by

Holliday, again, a very small study. So, the percentages, again, are probably a bit misrepresentative. There was a statistically significant difference, however, in the confidence interval up to 75 for the adjusted odds ratio suggest that the estimate is not stable. If we look at osteoradionecrosis one study a fairly reasonable size study did report based on grade of late toxicities over greater than six months, and we can see that again, there is no statistically significant difference between proton beam or the IMRT, but again, because of the study biases, we considered this to be insufficient evidence.

If we now turn to skull based chondrosarcomas, they are a little bit different type of tumor, and disease specific and progression free survival are on this particular slide, and there were no statistical differences for proton beam therapy plus surgery versus surgery alone and disease specific survival at five or ten years across all patients, but if they did . . . in their subanalysis of petroclival lesions, there was a little bit more pronounced effect, but again, the sample size is very small, and it was considered that the strength of evidence was insufficient. If we look at complications, and again a small retrospective study, of a skull based chondrosarcomas, you see that some are statistically significant different based on the type of toxicity that is reported. Most complications were more common with proton beam therapy, but again, remember, that's including surgery, as well, versus surgery alone. Any complication, hearing loss, and outcomes, and dizziness, were significantly higher with proton beam therapy, but again, the sample size is small, and the intervals for the crude relative risks that we calculated are very large. Again, the estimates were probably not very stable. If you look across case series, again, here is the range of the different toxicities and the different grades of toxicity. Sample sizes for most of these again were very small. So, detecting rare events was not possible. Again, the percentages may be [inaudible] because of the small sample size.

Again, looking across for late toxicities, the previous slide was early toxicities or acute toxicities, we see that the ranges are given here. This is across different tumor types. You'll notice that the two to five year rates for any late grade 3, those are for skull based chordomas and the others are for other types of toxicities.

Seth Schwartz:

Can I ask a little more detail about this question, because generally with chondrosarcomas, if it's a resectable tumor, patients may not get additional radiation. And oftentimes, you do an incomplete resection and then postsurgical radiation. So, the question is, is this a selected study, or how were these groups divided in this study? I mean, are we comparing apples to apples here is really my question.

- Andrea Skelly: You mean, in terms of what . . .
- Seth Schwartz: In terms of the overall survival and disease free survival, and then in terms of toxicity. Toxicity has become less important if it's not a choice. In other words, if you completely resected the tumor, then those patients have surgery and then they don't need it versus the other way around.
- Andrea Skelly: So, you're talking about the comparative studies?
- Seth Schwartz: Yes.
- Andrea Skelly: OK. I am going to have Erika help me with that, because she has the more nitty gritty detail about the studies on the skull based versus the . . . you're looking just at skull based or the, the non-skull based?
- Seth Schwartz: For the chondrosarcomas, I'm looking at the skull based. The question of the skull based chondrosarcomas.
- Andrea Skelly: So, there was one study of skull based chondrosarcoma. Only one study, and there was [inaudible] versus surgery alone. So, you want to know, to know to what extent there was total resection prior to that, or?
- Seth Schwartz: Well, I'm just trying to understand how they differentiated the groups. In other words, were they . . . was it prospectively decided that they were gonna do surgery, or was it simply that the patients got an incomplete resection then went on to have it? Or they selected the patients differently is what I'm trying to understand.
- Andrea Skelly: We can look up that specific study. Actually, we have a copy of that specific study that we did make a copy of. And we'll look at that, if you'd like to give us a minute. Or can we come back to that? What would you like to do?
- Seth Schwartz: Well, I'm just trying to understand what, I mean, either way, we can handle it, but I, but do you understand the point I'm asking. If you have a larger tumor that's unresectable, and then they need subsequent radiation, and they still have a better outcome, they're already bias against a good outcome. So, I'm just trying to really understand that data here.
- Andrea Skelly: No. I understand, and I don't have the answer off the top of my head. These were retrospective studies.
- Gregory Brown: There's no comparison . . .

- Andrea Skelly: No.
- Gregory Brown: . . . to regular [inaudible] radiation?
- Andrea Skelly: Not that we found. It was just versus the surgery alone. So, basically, that's the question, does the addition of proton beam therapy to surgery improve outcomes? I mean, that's kind of the underlying question here. I think Josh is looking up the specific study, which is the study by . . . I'm sorry what? Simon 2018. And do you have some information, Erika, or?
- Mika Sinanan: While we do the pause, I will note that this is one of the rare studies where surgery had significantly fewer complications than radiation. And I just want to make sure that we don't swipe right by that.
- Sheila Rege: I would like to take the time to ask our expert actually, but this is head and neck cancer. So, I don't [crosstalk].
- Smith Apisarnthanarax: I can do my best.
- Sheila Rege: OK. We've heard about the feeding tube dependence, and I'm looking at head and neck cancers and I don't think the studies parsed out the paranasal sinus or the non-ipsilateral oropharyngeal cancers or the nasopharyngeal cancers. In your [inaudible], which ones have you seen going to protons . . . do you have any thoughts?
- Smith Apisarnthanarax: So, definitely the . . . even though nasopharynx is not considered skull based, nasopharynx is definitely one of the tumors that we do treat a fair amount, just because of how central it is. It's really close to the skull base, and definitely there's a huge potential benefit there, you certainly see. Oropharynx, certainly the unilateral tumors. We certainly treat a lot of those, just because if you don't have to treat the contralateral oral cavity or neck, what better way to spare that than [crosstalk].
- Sheila Rege: [inaudible]
- Smith Apisarnthanarax: Yeah, but you still get a little [inaudible] to the anterior oral cavity and the other structures that are midline and past, but I had a question, actually. We haven't gotten to the summary slide. So, I'll wait.
- Sheila Rege: That helps.
- Andrea Skelly: Regarding Simon, as far as the inclusion criteria goes, they just say that all patients had surgical resection in their departments. And if you look at the

table one that lists the demographics, those who got surgery and proton had less, like, only 13% had a gross total resection, whereas 87% had partial; however, in the surgery only group, it's about half and half, 54% had a gross total, and 46% had partial. So, I don't know if that speaks to some of what you were trying to get at.

OK. So, moving on. I mean, again, the small sample size and the potential for risk of bias was high. So, we felt that the information was insufficient. The evidence was insufficient. I pushed the wrong button. We have gone over this particular slide for toxicities. Again, for acute toxicities, we [inaudible] slide pointing out again that the skull base chondrosarcomas show a different range of any grade 3 toxicity between two and five years.

So, we come to the only cost-effectiveness study, which was available, which is a different type of cancer altogether. It was oropharyngeal squamous cell carcinoma. The population was different. They modeled 65-year-old patients with stage 3 to 4B oropharyngeal squamous cell carcinomas and looked at proton beam therapy versus IMRT from a societal and payer perspective. Under both of those, even when they varied the assumptions to reduce the dependence of gastrostomy tubes and look at improved xerostomia, etc., the instrumental cost-effectiveness ratios were still not cost-effective. They were about \$100,000/QALY, and it was a very wide range. They did a lot of very good quality sensitivity analyses in this particular study and concluded that proton beam therapy was not cost-effective using either a societal or payer perspective. When you look at the extremes of superiority for proton beam therapy, it may be cost-effective for younger patients who are HPV positive. Again, the limitations are the oncological outcomes were assumed to be the same for all of the radiation therapy methods, despite limited evidence. They, again, modeled a lifetime horizon, but they were no longterm comparative data available. Societal costs were assumed to be the same for both treatment modalities, and they seemed to use an additive algorithm for accounting for toxicities for the disutilities, which may have biased the results a little bit. So, they have underestimated the QALY for IMRT.

Gregory Brown: So, am I reading the interventions right. One is proton beam therapy with chemotherapy, and the other is . . .

Andrea Skelly: Yes.

Gregory Brown: Radiation without chemo?

Andrea Skelly: I would have to look that up, but I would imagine that it also included chemo, as well.

Gregory Brown: OK. We'll have to look that up.

Smith Apisarnthanarax: I don't know the study in detail, but, I think they're comparing the differences in radiation.

Andrea Skelly: Radiation. Right. So, in summary, again, for head and neck tumors, again, recognizing this is the 30,000'th review, that the health benefit may be comparable, both in terms of benefits and harms. Again, I've highlighted this in the fact that we saw that we are dealing with different types of cancers, and very different types of studies. The benefits and the harms are a little bit more challenging, because of the differences in patient populations and interventions. So, this is something that needs to be considered.

Smith Apisarnthanarax: I have a question. So, basically, the summary was that the benefit was comparable, but just kind of looking at slide 64 and 65, and this was brought up by the head and neck experts in the public forum, was that there was a difference in G-tube dependency, as well as when you look at G-tube and weight loss. And I did note that written here, it says the differences may be clinically important. So, I guess, that's one thing that might be lost is that you can look at statistical significance, but if you look at, for example, the Holliday study for nasopharynx, it's a three times decrease, right, in G-tube dependency. So, I just wonder where it seems like there is at least some data to support that there might be a benefit. So, I just wonder where the comparable benefit is coming from.

Andrea Skelly: The comparable benefit comes from the overall survival, progression free survival. The harm piece would include the G-tube dependence. So, the overall net benefit could, again, there was an attempt to look across all toxicities and all things. Some are statistically significant. Some are not. Some may be clinically important. Some may be not. That's why I highlighted in that's something that maybe as a clinical expert can speak better to than the evidence vendor. So, again, it's trying to take into account those factors, in addition to the factor that these studies still have a potential for bias.

Smith Apisarnthanarax: Sure. Sure. And I think that's certainly . . . you have to take that into account, the size of the study and everything, but I guess when I look at net benefit, that includes both clinical outcomes, as well as toxicity. Is that correct?

Andrea Skelly: Yes.

Smith Apisarnthanarax: Right. So, obviously, there's no . . . you wouldn't necessarily think there was a benefit for survival, because we're given the same dose. Where the benefit is probably going to be in toxicity. So, it seems like there's some data to support that. Again, the termination at the level might be low. The level of evidence might be low, but there is some evidence and whatever evidence there is, it's quite marked in terms of the clinical difference. I think for head and neck, there's a lot of matrix that you look at. Right? You can look at mucositis grade 1, grade 2, grade 3, which is subjective, but whether you have a G-tube or not is not subjective. So, that's why, I think . . . anyway.

Gregory Brown: I would say let's leave that until the end of the presentation. Then, more when we have open discussion.

Smith Apisarnthanarax: I don't know how it works.

Gregory Brown: Sure.

Andrea Skelly: Yeah. Again, the Holliday study was a very small sample size and a very high risk of bias. So, yeah. We'll continue on. Alright, so again, now there may be some question whether the harms should be boosting that up to a different level versus a comparable level, considering the types of studies that we had to deal with. Proton beam therapy was not cost-effective in one cost utility analysis of squamous cell carcinoma in the oropharynx.

Liver cancer. We have a couple of studies. We have one of our only randomized control trials here represented, and it was against a case, which is [inaudible], catheter arterial chemoembolization, which may or may not be a commonly used treatment, and it's an ongoing trial, and these are preliminary results in 69 patients. Overall, there was no significant difference between the two treatments in overall survival, but proton beam tended to improve progression free survival compared with the case patients against statistical significance was not reached, and these are results, again, from an interim trial. Nonetheless, we felt that because of the quality of the trial, it was considered to be moderate evidence. The other study was a retrospective cohort study. Overall survival was significantly higher for proton beam therapy versus IMRT. So, strength of evidence was considered to be low. Again, looking at our RCT, the acute toxicities, there is really very limited information. They really didn't report on them. They used kind of a more of a surrogate of hospitalization. Significantly fewer patients who had proton beam therapy required hospitalization in the month following treatment versus the TACE patients. The total hospital days were significantly fewer versus TACE patients, but

again, this is from an interim analysis from an ongoing trial. In terms of acute toxicities, again, they really don't give us much information on that.

Going onto the next, again, from case series, again, we may be a little bit different. There are no comparators, but we've tried to separate that by curative intent, mixed curative intent, and metastatic tumors. You can see the range of toxicities reported in some of the case series. Again, most of the studies were small, but we tried to give a range where we could put the studies together.

For cost-effectiveness, for inoperable hepatocellular carcinoma, there was one cost-effectiveness study, which was very poor quality. So, inoperable advanced large hepatocellular carcinoma, they compared proton beam therapy versus FBRT. I would point out that the patient populations were very different in terms of their trial 2 class, and the sizes of the tumors and the prevalence of hepatitis C. So, they are very different patient populations that they're comparing for this. The bottom line was, they felt proton beam therapy would be cost-effective for inoperable advanced hepatocellular carcinoma at willingness to pay for the threshold in Taiwan. So, the question is whether or not that would be a valuable comparison for the United States. Again, the data were from case series and not particularly good data. There were substantial differences in the patients that were evaluated, and they really did not present sensitivity analysis well.

So, for adult liver cancers, again, we have very limited information from two studies, one RCT versus TACE and another one versus IMRT. In both instances, it appears that the benefits, in terms of overall survival and progression free survival may be similar, but proton beam therapy was associated apparently with lower toxicities, lower harms. So, there may be evidence for incremental benefit.

Compared to the 2014 report, there were three comparative cohort studies, and they felt that the benefits and harms were comparable. I would point out that they use this compared to photon therapy, chemotherapy only, and carbon ion therapy. Carbon ion therapy is not FDA approved. We did not include studies with carbon ion therapy.

Alright, moving onto nonsmall cell lung cancers, looking at overall survival. There were no statistical differences, again, between groups at one to five years and one RCT. Again, we thought that the strength of evidence was moderate because of the quality of the study across poor retrospective cohort studies. They were in alignment. Some of the differences, again, may be clinically important. If we take a look at other effectiveness

outcomes, cumulative incidence of local failure, there were no statistical differences at any time point in the one RCT. In the observational studies, that was basically a similar thing for recurrence free survival and for local failure, but for the small studies that were involved in the observational studies, we felt that the evidence was insufficient.

Looking then at the randomized control trial and then the retrospective cohort studies, looking at the rate of radiation pneumonitis at grade 3 or higher, there were no statistical differences between the two groups at one, two, three, four, or five years. We considered the strength of evidence to be moderate. Looking at the retrospective cohort studies, if we looked at grade 3 or higher, there were no statistical differences, but some, again, may be clinically important. Again, it's important to remember that small sample sizes may preclude finding rare events.

Again, for case series, this is the range of toxicities that were reported in the studies that we had available to us.

For late toxicities, here are the ranges, again, of the events that we had available to us, again, pointing out that many of these studies had very small sample sizes. And the followup for some of these was also maybe relatively low, like, 14 months for some of the hematological toxicities and one case series and other toxicities reported here.

So, for adult lung cancer the 2014 reports suggested that there were comparable benefits and harms for lung cancer. Our findings are consistent with that. We came to similar conclusions, and we did have an RCT to use, in addition to additional retrospective cohort studies for this evaluation. The previous report did include three large comparative studies, and they looked at proton beam therapy versus IMRT, 3DCRT, carbon ion. They felt the strength of evidence was low. We now have evidence from one RCT and five comparative observational studies. Again, thought that the comparable benefits and harms were consistent with what was found in the previous report.

If we move to ocular tumors and take a look at overall mortality and overall survival, there are two studies that were included. One was a fairly large study of choroid melanoma. The other was one of uveal melanoma. Again, we've got different cancer types that we're dealing with for these two studies. The study of choroid melanoma suggests that there may be a higher risk of mortality when compared with brachytherapy or mortality, but there was no difference at two years in overall survival for proton beam therapy versus brachytherapy or for mortality for proton beam therapy versus stereotactic radiosurgery in the retrospective cohorts;

however, there as a significantly higher risk of mortality for the proton beam therapy versus brachytherapy for the choroid melanoma patients. Again, that may be differences in radiation protocol, differences in adjunctive treatments, differences in cancers. It's hard to say, but the strength of evidence was low.

For adult ocular tumors, again, looking at the same situations using here . . . looking at uveal melanoma across a couple of different retrospective cohort studies, one versus stereotactic radiosurgery, one versus brachytherapy plus transcleral resection, again, may or not be something that's commonly done, but recurrence was significantly less common for proton beam therapy versus brachytherapy in conjunction with the transcleral surgery at all times, for all patients at three years, and there was no significant difference in the local recurrence for proton beam therapy versus stereotactic radiosurgery, but again, we felt that information . . . that the evidence was insufficient. In terms of studies that looked at metastasis, there was no difference at any time point in the one study that reported that outcome.

For adverse events, again, we have kind of a mixed picture. Optic neuropathy was significantly less common with proton beam therapy versus stereotactic radiosurgery, but there were no other statistically significant difference for either of the retrospective studies represented here for the other outcomes that we see, which included neurovascular glaucoma, rubeosis of the iris, and enucleation.

Again, case series provide information on the range of rates for various complications, various toxicities, and you can see that there is a fairly wide range. There was most evidence from case series in 14 case series with over 7,000 patients that suggested enucleation, while it occurred in up to 16% of patients and that was the most information we had from some of the case series. You can see what the rest of the ranges of the toxicities were from the case series.

Event probabilities, five year enucleation free survival was high across three case series. You can see that some of the other things were also very high for retinopathy free survival and optic neuropathy free survival were very high with proton beam therapy and incidence with cataracts varied by year, increasing by the years that were reported. Again, these are from case series. So, we don't know what would happen with other comparators.

There was one cost-effectiveness study done in the U.S. that was of moderate quality that looked at patients 59 years of age with intraocular

melanoma. Again, we're talking about different tumors than some of the cohort studies. They only looked at a five-year time horizon, which may be reasonable. They modeled a variety of parameters, and they found it was not cost-effective compared to enucleation at a willingness to pay of \$50,000/QALY, but the results were not robust to sensitivity analysis and showed that if you decreased the payment rates for proton beam therapy, it could result in proton beam therapy being dominant over enucleation. Again, the problems associated with this were the use of data that didn't have longterm information, but actually looked at more case series types of data. The assumption that they have about cost seems to be kind of very strong assumptions, and the frequency of enucleation for treatment as a treatment option is not clear in this day and age. So, some things to consider there.

So, in terms of overall summary for this, the previous report, there was a discrepancy in the report executive summary compared to what the report had in the main body of the report regarding the net health benefit for proton beam therapy versus comparators. The previous report had indicated that proton beam therapy had a superior net health benefit, because it increased benefits and decreased harms, and the strength of evidence was moderate. If you look at the rest of the report and look at what they have in their other table, they said it was an incremental benefit. It's unclear from my standpoint how they came to that conclusion. When we looked at the data we had available, we found that by comparator, there were maybe some different conclusions. When we looked at proton beam therapy versus brachytherapy alone, it did not appear that there was net health benefit from the standpoint of benefits were lower, and harms were comparable. However, when you look at proton beam therapy versus brachytherapy, both with transcleral resection, it appears that there might be an incremental benefit, in terms of survival related outcomes, but the harms were comparable. With the stereotactic radiosurgery, there was insufficient evidence to draw conclusions. There was one economic study of reasonable quality, but proton beam therapy was not felt to be cost-effective for a variety of reasons, but the results were not robust to sensitivity analysis. So, I would like to point out a couple of things in terms of comparison to the 2014 report that are important to remember. One of the things is that there was substantial differences in the comparators that were used in the previous report compared with the comparators that we had available in the literature that we included. In addition, there were differences in probably the protocol for proton beam therapy and you can see that enucleation there were four studies in enucleation in the 2014 report. We didn't have any studies of enucleation here. So, it's been very difficult to compare the two reports in terms of the findings for the net health benefits, because of the differences

in comparators between the two studies and the types of studies. They used two studies that were nonconcurrent control studies. In other words, they compared basically two case series. So, again, it's very difficult to extrapolate between the two reports for this particular set of tumors.

Are we ready to tackle the prostate? OK. I'll tackle the prostate. So, in terms of prostate, we have one study, which was of reasonable size [inaudible], which was a quasi-RCT, which means that the randomization was not appropriate for this particular setting. We look at the probability of overall survival, as well as the probability of biochemical free survival. There were no statistical differences between proton beam therapy used as a boost with photon therapy versus photon therapy alone. Some of these differences are very close. So, again, clinical significance may be indistinguishable and something the clinical expert can maybe speak to at some point. If we take a look at toxicity from the quasi-RCT, we see that the toxicity for photon plus proton beam therapy boost versus photon early, there was less gastrointestinal, genitourinary toxicities acutely, looking at the frequencies for acute, as well as for late toxicities. The late toxicities, the differences aren't as clear, and the actuary or frequency of GI and GU toxicities works better than grade 3 was different in the studies, as reported, but again, they did not report statistical significance. So, clinical significance wouldn't maybe need to be considered here, but again, most of these did not reach . . . some of these did not reach statistical significance. If we look at the retrospective cohort studies, we see again that there may be [inaudible] where some of the toxicities to be acute and late.

Gregory Brown: I'm sorry. Can you go back one.

Andrea Skelly: Sure.

Gregory Brown: So, there are eight comparisons up there. Correct? Grade 2, or grade 3, 4.

Andrea Skelly: Right.

Gregory Brown: Gastrointestinal, genitourinary, or acute versus late. So, two to the third power is eight.

Andrea Skelly: Yes. Thank you.

Gregory Brown: So, you did a Bonferroni correction. The P value would be closer to 0.005.

Andrea Skelly: Potentially.

- Gregory Brown: OK. Well . . .
- Andrea Skelly: Potentially.
- Gregory Brown: . . . so, but the point is that if you start doing multiple comparisons, you shouldn't be using 0.05 as your level of significance.
- Andrea Skelly: Exactly.
- Gregory Brown: Correct?
- Andrea Skelly: Yeah. Right.
- Gregory Brown: So, your probability of finding a . . .
- Andrea Skelly: Statistically significant . . .
- Gregory Brown: . . . non, well a non, a type 1 error.
- Andrea Skelly: . . . yeah. It's much higher.
- Gregory Brown: Is much higher. So, with the Bonferroni correction, would that 0.01 likely to be clinically significant, or statistically significant?
- Andrea Skelly: I would not want to venture to say because of the quality of the study and potential for bias. Statistical significance can be very much impacted by the differences in patient populations that are not reflected in whether or not you do a Bonferroni correction or not. It is possible that maybe it would be closer to statistical significance, but I think given the quality of the studies, I would be very hesitant to say, yeah. Let's hang our hat on that.
- Gregory Brown: OK. Thank you.
- Andrea Skelly: Mm-hmm. OK. So, again, looking at acute and late toxicities across two different retrospective cohort studies. Again, we see that there is maybe a tendency for some of the toxicities to be somewhat lower for proton beam therapy versus IMRT. Some of the differences are not huge. Most of them are not statistically significant. We've got one small study and one moderate sized study to look at. Unfortunately, the studies look at grade 2 or 3 versus grade 3. So, again, it's kind of hard to assess how to compare these to some extent.

So, we have a retrospective database study, again by Pan that looked at a very large number of individuals and a large number of individuals, a lot of things become statistically significant when they may not have otherwise been. They look at 693 patients with proton beam therapy versus 3465 IMRT recipients. In terms of the late urinary tract toxicity of any grade, again, we tried to focus on grade 3 or higher, but they didn't give us that information. There was a statistically significant effect looking at preferring proton beam therapy for late urinary tract toxicities. Late bowel toxicities, it was marginally statistically significant; however, the [inaudible] ratio does potentially include one if you round. There was erectile dysfunction as one of the outcomes, but again, there appears to be a statistically significant impact. The proton beam therapy again being favored. Again, very large studies, sometimes, things tend to be statistically significant, and that's something to consider.

Gregory Brown: But the middle one favors IMRT not [crosstalk].

Andrea Skelly: Thank you, yes. The middle one does favor IMRT. Thank you for pointing that out. Again, the strength of evidence was low. As you pointed out, we've got some conflicting information about the safety and toxicities across the different types of toxicities. Again, in case series, we see that there is a range for different types of toxicities for proton beam therapy only. If we look at acute, that's separated out by late toxicities. One study, again, with a fairly large number of individuals found that the rate of incidence of late grade 3 GI toxicities was less than 1% and a higher rate of late GI toxicities of grades 1, 2, or 3 over five years tended to diminish, and the same thing with the late genitourinary tract toxicities. The key relative incidence of the Argon plasma coagulation application for rectal bleeding was 5.6%. Again without comparators, it's hard to know how that would compare to other radiation therapies. We did include contextual studies for the prostate. These were the ones that looked at some dosimetry information and then provided information on variant outcomes. We did not do strength of evidence for these studies. One study looked at the RCT and then there was also one retrospective cohort that showed no difference between groups and quality of life. They used various measures. [inaudible] toxicities.

There were no treatment related deaths. That was looking at hypofractionation versus standard fractionation. Again, there were different kind of dosing opportunities for moderate versus extreme hypofractionation in one RCT. At 70 years, there was a 97.5% overall survival in the entire population. There was statistically lower for the EHF group. The [inaudible] ratio was statistically significant. There were no differences in acute or late toxicities in this particular study. Looking at

passive scatter versus spot scanning technique in one retrospective cohort, there were no differences in groups in quality of life or the frequency of genitourinary tract or GI toxicities, but again, we did not do strength of evidence for these studies that were included for context.

In summary, consistent with the 2014 report, based on the evidence that we found again conflicting evidence related to toxicities. We felt that the benefits and harms were, again, comparable and the strength of evidence was low.

So, in summary, for adult conditions and tumors, compared to the 2014 report, there are 37 new comparative studies that were identified, again, most of them were retrospective cohort studies at moderately high risk of bias. The new studies identified for some tumors and conditions replaced studies that had only case series from the previous report. Some of them were insufficient then, and now have additional evidence. We identified four new cost utility analyses in adult tumors. The strength of evidence was low for all conditions and outcomes with the exception of the one study of hepatocellular carcinoma and had randomized control trial. The comparative net benefit based on new evidence changed for some conditions. The differences in comparators and tumor types, again, needs to be considered, as well as the difference in application of proton beam therapy. The approaches and studies in the previous report, again, may be very different, and that may partially explain why the net health benefit may appear different based on the studies that we included. No studies permitted evaluation of differential effectiveness or safety.

So, in summary, there were no comparative effectiveness studies for bladder cancer, bone cancer, lymphoma, benign tumors of any type, or various mixed tumor types. There was no evidence meeting inclusion criteria for sarcoma, seminoma, thymoma, or AVMs in adults. The net health benefit for proton beam therapy was considered to be incremental to other treatments for esophageal tumors for liver tumors, and for ocular tumors. The net health benefit of proton beam therapy was considered to be comparable to other treatments for brain and spinal tumors, head and neck tumors, and focusing on the non skull based tumors, lung cancer, and prostate cancer, and for the one comparator for ocular tumors, brachytherapy alone, the net health benefit was considered to be inferior. There is insufficient evidence or unclear evidence of a net health benefit for salvage and brain and spinal tumors, for pancreas tumors, or for breast cancer. For chondrosarcomas, again, the evidence was considered insufficient. For the comparison of proton beam therapy versus stereotactic radiotherapy, the ocular tumors, again, the evidence was considered to be insufficient. For the economic studies, conclusions were

really limited, because of the hypothetical models and the limitations associated with them, and the fact that most of the data . . . all the data were derived from case series, some of them very small. Many of the models did not fully specify factors that may impact cost-effectiveness or describe the changes in patient situations longterm. Some of the sensitivity analyses suggest substantial variation in cost-effectiveness.

In terms of general summary, both reports focus on comparative studies. The evidence base for comparative studies, again, was mostly retrospective cohort at moderately high risk of bias, including selection bias, attrition bias, and confounding. The RCT's may not be ethical or feasible in some populations. Again, we attempted to account for that with the [inaudible] that we evaluated and used the grade process. The strength of evidence did take into account the lack of RCT evidence and the challenges; however, again, um, it needs to be remembered that non-randomized studies, the quality of them is not elevated in this situation, and that the greater uncertainty related to the potential for bias, the biases listed up above, needs to be considered in the decision making.

In terms of comparators, again, comparators and tumor types were different between the two reports, and that needs to be considered, as well. There is substantial heterogeneity across all the 200 and some studies, both in tumors types, as well as how proton beam therapy was used, as well as adjunctive therapies. So, it's very difficult to synthesize across the heterogeneity. In addition, over 150 case series of many different tumor types, some are rare, some are maybe more common, were included, but they do not provide information on comparative effectiveness or safety. So, my gecko friend says, it's time for lunch.

Kevin Walsh: Can we go to page . . .

Gregory Brown: Could I interrupt just a second. We've got ten minutes to lunch. So, do we want to break now for lunch and then do it afterwards, as opposed to get into for ten minutes, or? Sure. Sure.

Kevin Walsh: I propose that we finish the report, break for lunch, and then start our discussion.

Gregory Brown: OK. Perfect.

Kevin Walsh: Thank you. Could I ask you to go back to slide 91. This is in reference to your summary slide, 102, which describes an incremental benefit to proton beam therapy in ocular tumors. My reading of this slide is not as enthusiastic as yours. Can you help me understand why . . .

- Andrea Skelly: For our . . .
- Kevin Walsh: So, you're . . .
- Andrea Skelly: 2019 conclusions, as opposed to 2014?
- Kevin Walsh: . . . in your summary on slide 102, you're proposing that there is a net health benefit to proton beam therapy in ocular tumors.
- Gregory Brown: Slide 102.
- Sheila Rege: It's the summary. So, here.
- Andrea Skelly: We said there was incremental net health benefit to proton beam therapy for ocular tumors based on the comparison of proton beam therapy versus brachytherapy versus having transcleral resection. So, it's specific to that particular type of comparator and benefit. Slide 91, and if it's inconsistent, we'll take a look at that. Slide 91 . . .
- Kevin Walsh: I misread your conclusion on slide 102. I'm sorry.
- Andrea Skelly: OK.
- Kevin Walsh: So, you're saying, specifically for this, there's incremental benefit, but overall . . . I'm a little confused, because 102 is a summary slide, and you're getting into a much higher level of granularity in your statement.
- Andrea Skelly: OK.
- Kevin Walsh: You're calling it a benefit only in this situation?
- Andrea Skelly: Well, there is incremental benefit for the middle comparator.
- Kevin Walsh: Correct.
- Andrea Skelly: There is inferior thing for the other comparator, for the proton beam therapy versus brachytherapy alone.
- Kevin Walsh: So, that to me says one shows benefit and one does not. Am I completely incorrect?
- Andrea Skelly: Meaning you're trying to create a summary across those two comparator types. And I . . .

Smith Apisarnthanarax: I think he's asking why in your summary slide your recommendation is generalized. Is it generalized or is it specific . . . for 102?

Kevin Walsh: Correct. Thank you.

Andrea Skelly: That is specific, I believe. It was intended to be specific.

Gregory Brown: She does. She said . . .

Andrea Skelly: For the . . .

Gregory Brown: . . . you know, transcleral . . .

Andrea Skelly: . . . proton beam therapy versus . . .

Gregory Brown: . . . resection in that.

Andrea Skelly: Yeah.

Gregory Brown: For, or [inaudible] tumor. She's specific on 102 there.

Andrea Skelly: Yeah, but it's for that comparator. And it's inferior for the comparator compared to brachytherapy alone. So, this should correspond to what is on slide 91. And if it isn't, let me know. So, we said that there was an incremental benefit versus brachytherapy when both groups had transcleral resection versus stereotactic radiosurgery. There was insufficient evidence. Then, for proton beam therapy versus brachytherapy alone, it was inferior. And because of the differences in the comparators, I don't feel that it's appropriate, personally, to draw a conclusion of a net health benefit overall.

Kevin Walsh: Thank you.

Andrea Skelly: Yeah. OK.

Smith Apisarnthanarax: There was no mention or comment on re-radiation. Is that because there was nothing new in the past five years, or you weren't tasked to review that?

Andrea Skelly: Our search criteria was very broad. Again, we looked at the citations that were put forth for our consideration. They did not usually talk about re-radiation in terms of comparative studies. Erika can speak to this a little bit, because she helped a lot with some of that. For salvage and for

recurrence, we reported what we had. That, to me, may have not been a total re-radiation issue.

Smith Apisarnthanarax: The reason why I ask is, because it was reviewed in 2014, but it wasn't reviewed in 2019. So, I was just wondering why.

Andrea Skelly: Yeah. It's probably because there wasn't new evidence. So, Erika did you have information other than that?

Erika Brodt: We didn't exclude anything. We would have incorporated that. So, I can go through again and look and see if any of the populations, if they talk about in the inclusion . . .

Smith Apisarnthanarax: It's an unusual category, because it's not disease site specific. It's just . . . because re-radiation is almost like clinical context rather than disease type, but I wasn't sure whether there was nothing that met the criteria or maybe it wasn't specifically honed in on.

Erika Brodt: Well, I can [inaudible] that the search was incredibly broad, and we tried to include everything we could that met the inclusion criteria. So, we wouldn't have excluded any for that reason, unless they didn't meet other inclusion criteria.

Andrea Skelly: It is possible that some of the case series may have represented instances where there was re-radiation. Without going through the 150 of them, it would be hard for me to say.

Smith Apisarnthanarax: Or whether it didn't meet the threshold number of patients or that sort of thing?

Andrea Skelly: Yeah. And for information in the full report, we do list the reasons for exclusions of the text, and if there had been something of full text that was comparable in a comparative study, it would have been included, and none of the public comments or other comments suggested that we had missed a re-radiation study.

Gregory Brown: Other questions? OK. Well, thank you.

Andrea Skelly: Thank you.

Gregory Brown: So, do we need to have a separate lunch or working lunch after we get food and start a discussion? Committee preference?

Tony Yen: I'd like to have a working lunch if at all possible.

Gregory Brown: So, 15 minutes to get our lunch and sit down. And then, we'll start discussion? So, I have 12:42. So, how about 1:00. Is that OK?

OK. I think we are . . . we got all the committee members here, except for a member who is at home on the phone. So, maybe we could unmute the phone for her. While we're doing that, anybody want to start out? Tony?

Tony Yen: Well, I have a question for our expert, Jim. The physics behind this is really interesting, proton beam therapy versus photon beam therapy. What's kind of just having just some very superficial appreciation of the physics behind it, I'm kind of curious, why is it that I don't see a really marked difference in terms of overall clinical outcome or a marked difference in decreased toxicity. We see some . . . I think the literature that we have in front of us shows some decreased toxicities for, like . . . requiring PEGs, maybe decreased mucositis, but kind of on the one side of knowing the physics with a lot of the committee members overhear the speakers in the audience coming up and showing us dose maps. It would be super compelling to me, but yet I don't really find that marked difference within the literature that we have. Do you know why that might be so?

Smith Apisarnthanarax: I think it's hard to make a blanket statement about protons for everything. It really does depend on the disease site, what you're using it for. Obviously, in pediatrics, it's . . . when you talk about late effects especially, it's very hard to get that data, because you're looking at late effects, five, ten. These patients grow up. They go away. You may not be able to capture some of those patients. Disease in esophageal, as an example, it depends on how you're using the radiation. So, there is some data for esophageal that does reduce perioperative outcomes, but I think anyone who tries to do research on reduced toxicity, it's very subjective. So, some of that gets clouded, as well. I think as we do all do randomized studies, we always pick the most unequivocal endpoint, which is survival, but that's not always necessarily the endpoint that protons are designed for. So, if you're looking at toxicity, the challenge is to really find that toxicity metric that is going to be robust and is non-subjective. Right? It's easy [inaudible], like, was that a grade 1, grade 2, grade 3? So, then historically, if you're looking at a case series, retrospective has been pointed out, it's difficult because the patients are heterogeneous, as well as our selection bias. Just to give you an example, sometimes, we treat the sickest patients with protons, because no one else wants to treat them with IMRT. So, inherently, we see the same thing in liver cancer. Unless you really control it, we treat only the sickest liver cancer patients, because the surgeons don't want to touch them. Interventional radiologists don't want to touch them. So, they come to us. So, there's already a selection

or referral bias. So, it's challenging. I think that everyone is doing their best to gather as much data as possible, and I think that was clear with all the speakers. The challenge is getting that data, and you can't do randomized trials for everything. Right? So, I think each disease has their own challenges, basically to answer your question, in terms of actually getting the data that we want to see.

Tony Yen: No. I understand that, but I would think, you know, with just the physics behind it and the basic science, as you mentioned before, I would see a huge difference, a huge difference. And there's differences that, I think, at least the literature presents to us. There are either fairly small numbers with some significance, or there's really not a whole lot. There's equivalency.

Smith Apisarnthanarax: I wanted to just clarify a couple things. 'Cuz I phoned a friend for some of the peds questions. 'Cuz it's been a long time, since I treated peds. I think Dr. Sinanan had a question about the trajectory of some of the late toxicities with endocrine and thyroid. So, you're gonna see thyroid and endocrine abnormalities dysfunction within three, four, five years. And so, it is well within that time period, although you probably will continue to see a little bit of uptick in dysfunction, as you go along, but as I mentioned before, there are things like sterility and cardiac toxicity that you're not going to see probably . . . and secondary malignancies until decades out. So, there are other things that may not be captured within that followup period. Does that answer your question?

Mika Sinanan: Yes. Thank you.

Gregory Brown: Anyone want to volunteer as to what they're thinking?

Kevin Walsh: I'd like to propose that we talk about pediatric, as a distinct set. Then move into the list of adult. I'm doubting that anybody has a generalized opinion about a thumbs up to all or a thumbs down to all?

Gregory Brown: For pediatrics you're saying now, or for just in terms of?

Kevin Walsh: For all.

Gregory Brown: OK.

Kevin Walsh: So, I'm assuming that. And if my assumption . . . if people don't share my assumption, then let's do a blanket . . .

Gregory Brown: That's reasonable. Anybody have any objections to starting with peds.

Group: No.

Gregory Brown: Yeah. So, OK. So, who wants to comment on their thoughts on peds?

Smith Apisarnthanarax: One can certainly focus on the data that we have in hand, which is the charge, but I think just in general, you have to still look at the clinical context of what we know and what we don't know. Right? There's certain facts that are undisputed, or else people wouldn't be trying to get radiation therapy for cancers, and that's the trend. Right? So, for lymphomas, the trend is to get rid of radiation. Why? It's because it causes toxicity. It causes cardiac dysfunction, particularly in the young lymphoma patient. That's not something, it's not disputable. So, to unnecessarily give radiation to a 5-year-old heart, you're not going to really get that in the data, but we know that that's just not a good thing. So, I think, as the committee looks at that, I think, yeah. You can focus on what's here in the last five years, but you also just have to look at the history of what we do in radiation oncology, and however you guys decide that, but I just wanted to kind of just bring it back into context.

Seth Schwartz: I have a slightly different approach on this. When I'm thinking about this is, to me it really sounds like a different tool for achieving the same thing. And so, I almost don't really expect to see superiority of protons over photons for cure or for disease free survival. It's almost a non-inferiority argument when it comes to what I want to see. And I think for the majority of the data, at least with regard to the pediatric side, we saw that, that there wasn't, like, an improvement in outcomes with the protons, but it certainly wasn't any worse. And there was at least equivalence or possibly a little bit better was the general sense I got, as far as the effectiveness of that therapy. So, I think what's clear is that the big question is, would I do it over photons, and it's because of this potential decreased risk of toxicities. I think we didn't see as much strength of evidence for that, as we would like to see. There's some, but I think it's pretty clear that the challenge here is that these kids are going to live a lifetime and be exposed to that risk whatever it is, and that these studies didn't really have the ability to document that, as an outcome. It's pretty well established for general radiation therapy. So, I'm feeling pretty good about that. So, I guess, and then the next step is so then, why not make this available? Really, the only question is cost. I'm struggling . . . I'm really struggling with the cost data that we're looking at, because we heard from the Mayo Clinic, and other pretty reasonable places that it actually may be more cost-effective than photons. Yet, we're not seeing that at all from the data. The data is . . . the cost-effectiveness data number one didn't look at kids. So, we don't have anything there.

- Gregory Brown: Can I push back on that a second? So, I heard two people say that it was cost-effective. They showed no data. It's a vague statement.
- Seth Schwartz: I understand. And I'm not arguing that they're right. I'm just saying that we're hearing different things. With regard to pediatrics, we don't see any data at all regarding cost. So, my point is, I don't know where we are on cost for this.
- Sheila Rege: Mayo was in the news, and I don't know if it's still true, that in 2013. They would charge insurance companies the same rates as IMRT for protons.
- Gregory Brown: So, actually, I . . . that's . . . I think, I align with you very similarly, but with that issue. So, to me, this is an artificial problem. This is an issue, because industry set a price that, to my understanding, at least in some cases, is five times more expensive than IMRT. And if they were simply codes for billing, radiation therapy, be it IMRT, be it proton beam, whatever, and there was no cost differential, everyone around this table would say, it's an appropriate form of radiation therapy, but there is no evidence for this dramatically increased cost, in terms of better outcomes. There's the theoretical fewer toxicities, which are hard to document. And, and so industry has created this conflict. I mean, again, I think everybody in this room would be agreeable to say this is an acceptable radiation therapy, if it were billed as every other radiation therapy.
- Seth Schwartz: Well, I think that's right, but I think part of what I'm struggling with is, we're not getting data on what the cost is of photons. Right? They didn't show us that. We're seeing the cost of proton therapy coming down over a three-year period, basically cut in half. So, I don't know what's happening with the cost of this. So, because, as you said, I think most of us are convinced that this works, at least as well as photons do presumably, and the toxicities are at least equivalent, if not better, in most circumstances. That it's reasonable. So, I'm a little stuck with this question of cost that I really don't know what to do with, because I don't what it . . . I don't really have a handle on what it is. I don't think the data that we saw gives us a good handle on what it is. And I don't think we know which direction it's going necessarily.
- Chris Hearne: I'm new. So, can I ask a generic question? Obviously, the rereview is focusing on the last five years. Is the committee purely looking at that? Or are they looking at what the data was prior to that and what would it take to reverse a prior recommendation? What's the threshold for that, because my understanding is you're focusing on peds, that it was recommended prior.

Sheila Rege: 2014. Yes, it was.

Chris Hearne: So, is the data now so overwhelmingly negative that it's going to completely reverse that? I guess, and that would apply for all that we talk about today is that how do you guys go about that, I guess?

Gregory Brown: That's a procedural question. That's appropriate. The answer is, it's up to us, but I think the point that is the new evidence, since 2014, compelling enough to change a previous recommendation? Is there reasonable threshold for us, but we all, again, we are chartered, as individual committee members, to review the evidence as a whole, or individual diagnoses, or whatever, and we come to our own conclusions. I mean, are there comments on that as a threshold? Is that a reasonable threshold?

Chris Hearne: In my mind, we would have to, in order to go back and narrow the scope of the coverage decision from 2014 to include CNS tumors, we would have to see in this past five years, in the rereview, some evidence. Some evidence suggesting that it only works in that subpopulation. I think what we've seen is just the only thing that we saw a lot of data on were the CNS tumors. We didn't see evidence that it doesn't work in other settings. No evidence at all, or very little.

Gregory Brown: To change our decision, or maybe say it another way, to change our decision, we would need to see significant evidence that proton beam therapy is harmful. [inaudible]

Chris Hearne: Or another way is the absence of data.

Sheila Rege: Before we go to process, can I answer Seth's question a little bit about what's maybe a cheaper? So, it used to be the proton facilities were huge. Now, there's these new companies. I think Boston was the first one, where they're shrinking their footprint. Jim can probably answer this more, needed for proton machines. So, it's miniaturizing and it's just making it a lot less expensive to build, which is why there is a lot of movement on new facilities if this works, this building smaller facilities rather than huge facilities with three or four rooms. Did that answer your question?

Seth Schwartz: I wasn't really asking the question. I think the point is, we don't know. I mean, I think that's a valid point that that may be one of the cost drivers, but the bottom line is, we don't know what the numbers are was sort of my point, which is that we don't have . . . we can sort of assume it's more expensive, but beyond that, we don't have a great handle on what the cost really is.

Sheila Rege: Now, we're in the process question. Yeah.

Smith Apisarnthanarax: So, this is going back to Chris's point. If there wasn't a lot of data just in the last five years. Nobody published on it, on non-CNS peds. This is the absence that no one did anything enough to reverse what was recommended before. That's the crux, I think. Now, if there's evidence that, oh, this is [inaudible] horrible. It's useless or, I mean, it's worse. We cause more cancers in kids, or whatever reason. I guess that's sort of what we're getting at right now.

Chris Hearne: And I think for me, the absence of evidence is not enough to go back on what was previously determined. The standard has been set in the 2014 coverage decision. We don't have evidence against that. So, in my mind, we would have to have that in order to kind of narrow the scope.

John Bramhall: So, there might be a pragmatic, almost an empiric element to it in terms of capacity. So, Jim, can I ask you, so this is not an academic question, but what's the capacity of the equipment that we have in Washington State? Is this running day and night 24/7, in which case it might be necessary to prioritize the cases that are presented for this therapy. If it's open and operating two hours a week, then you don't need to prioritize. You just need to demonstrate utility.

Smith Apisarnthanarax: Are you talking about peds or [crosstalk]?

John Bramhall: I'm thinking just in general principles.

Smith Apisarnthanarax: In general, oh.

John Bramhall: If you keep running all the time.

Smith Apisarnthanarax: Right. So, we're not running at full capacity, nowhere near it. As far as peds, they pretty much priority over any other case, because as was shown by the medical director, we have, like, a five step review process. As part of that process, it's priority utilization. So, if there's a time crunch in terms of slots for theoretically, we have an internal triage process where the highest risk cases, like peds, there's no question within oncology that the need for protons for kids overrides those in adults, just, I don't think anybody's going to [crosstalk].

John Bramhall: But if, [inaudible] question, but if cost constraints were removed, do you think that, I mean, is it possible to predict how much increased business there would be on the machine for pediatric? I'm assuming at the moment

that pediatric treatment is constrained to some extent by costing and by payment policies, because that's why we're here.

Gregory Brown: But it's currently covered.

John Bramhall: So, you wouldn't increase the number of pediatric presented. It could only decrease if we made . . . is that right?

Gregory Brown: It would be neutral. I mean, I don't . . . we don't, you know?

John Bramhall: You don't know?

Gregory Brown: All sorts of factors may increase or decrease it, but again, it's essentially no change in our policy. So, it shouldn't [crosstalk].

John Bramhall: So, at the moment, it's unconstrained by cost issues for people . . .

Gregory Brown: Yes, for peds.

Smith Apisarnthanarax: so, nothing was changed in the policy, there have been no other changes in other insurance policies. So, everything would be kind of neutral, unless there's more cancer in kids for another reason.

John Bramhall: I'm sorry. Not to monopolize, but that, that gets at this next element. If there's no cost constraint, then the number of kids . . . the cases that are presented, the pediatric cases that are presented for beam therapy of this sort, are decided objectively? Is that a reasonable assumption? They're decided on the basis of the therapy to value to that particular child with that particular disease? Or is it more . . .

Smith Apisarnthanarax: Yes.

John Bramhall: . . . capricious than that?

Smith Apisarnthanarax: It's always case by case, and [inaudible] the pediatric radiation oncologist, there are cases where he doesn't recommend protons, in spite them being referred for protons. So, it's always case by case. And it's always the best. As we do for all our patients, it's a combination of clinical judgment and what's out there in the literature and what clinically makes sense.

John Bramhall: And is it, so . . .

Gregory Brown: It's like most cancer treatment where it's multidisciplinary groups. They review patients.

John Bramhall: . . . is there a constraint currently, in terms of the structure of the studies that people might want to enroll pediatric cases into?

Smith Apisarnthanarax: Prospective studies? Well, any studies, it's . . . no. I think whenever we have . . . whether it's a cooperative group or whether there are studies, we always consider enrolling pediatric patients in clinical trials, if it's appropriate.

John Bramhall: Well, that's what I mean, if it's appropriate. So, I mean, is, theoretically, is there a child referred from Eastern Washington through the facility who doesn't meet the criteria for a study, is that child more or equally likely, or less likely, to actually receive the therapy?

Smith Apisarnthanarax: Well, I would say that just because of . . . a child is not a candidate for that clinical trial doesn't mean they're not a candidate for protons. They just maybe don't meet the eligibility criteria for that specific trial, but the decision to treat protons is independent.

John Bramhall: Independent. OK.

Kevin Walsh: I want to respond to Chris's procedural or process question. I disagree that there has to be overwhelming evidence that disputes the prior decision in order to come to a different decision about what the evidence says. So, I think if we read the evidence differently, than the group who sat here in 2014 reads the evidence, then we decide . . . we make a different decision. It's not like legal precedence. That's my opinion. There's not anything written that supports either of our opinions.

Gregory Brown: I agree completely.

Laurie Mischley: I just have a question for the HCA about . . . I think Seth was incredibly articulate in painting a picture of this being almost a non-inferiority decision and it coming down to cost, and us not having the cost data. What would be required for us to get those data?

Andrea Skelly: So, roughly, you're looking at the peds schedules, which I did on the break a little while ago. Some of it depends, because there are different intensity levels and complication levels. So, I'm not sure that we can say sort of apples to apples what it looks like, but in sort of rough numbers on the Medicaid fee schedule side, it looks like it's somewhere between and third and 50% higher for proton beam therapy versus IMRT and other therapy

would sort of, some of those caveats. Then, Josh also sent me a Medicare reimbursement bulletin. From 2017 to 2018, cost for proton treatment went up about almost 6%. So, the Medicare fee schedule is going up, even if sort of our overall reimbursement is going down. It really depends on the type of therapy that you're comparing it to, but I would say, it's roughly in that same category as somewhere between double more expensive and maybe, like, a third more expensive, randomly, not using [inaudible] scientific rules.

Gregory Brown: So, I would say that 33% to 100% more expensive? Is that what . . .

Mika Sinanan: 50%.

Gregory Brown: For Medicaid, but for Medicare, and what about under Unified Health Plan? I mean, that's kind of . . .

Andrea Skelly: There we go. UMP is not [inaudible]. So, we'd have to ask Regence what their fees are. I don't know if there's any secret sauce, or if we can just pay.

Mika Sinanan: Kind of a different take on this. Dr. Rankin, in his comments, made, in the second slide, there is no benefit to radiation to normal tissues. No data, but are we generally agreed that that is true? Jim, comments?

Smith Apisarnthanarax: I certainly would not want radiation [crosstalk].

Mika Sinanan: Well, that's a different question.

Smith Apisarnthanarax: Well, I would actually ask anybody if . . .

Mika Sinanan: But that's a different question. The data?

Smith Apisarnthanarax: Yes. There's no medical benefit to getting radiation to areas that don't need it.

Mika Sinanan: The implication, though, is that any degree of radiation is damaging to normal tissues, or harmful. Is that true?

Smith Apisarnthanarax: It depends on the endpoint. So, high doses to a normal organ, it really depends on the organ, as well, is different than low doses to an organ, but, for example, we know low doses to the brain is very damaging. Low doses to lungs, the GI, but low doses to your arm may increase the risk of secondary cancers, but probably not going to hurt your muscle. Right?

Mika Sinanan: So, differential damage, but, as far as we can tell, some degree of adverse impact from broadly speaking any degree of radiation?

Smith Apisarnthanarax: yes.

Mika Sinanan: And then the information that we have about longterm consequences, harms in kids. This gets back to our previous discussion about the timing of endocrinopathies and other side effects. It's really a point in time we don't have the longterm secondary cancer risk of proton beam therapy relative to other things. We don't have, in fact, any really longterm effectiveness data. Because we assume that there is some degree of harm to any tissue, and we already have evidence that there is damage, we could presuppose or infer that there is likely to be a progressive, to some degree, increase in harm over time, beyond what the data that we have shows?

Smith Apisarnthanarax: So, we know that radiation exposure to kids causes cancer. That's not disputable. Right?

Mika Sinanan: Well, not in the data that's been presented to us.

Smith Apisarnthanarax: Right, but we know from . . .

Mika Sinanan: Tumor field is indisputable.

Smith Apisarnthanarax: . . . well, yeah. That's why we, yeah. So . . .

Mika Sinanan: That's what I'm asking. Yeah.

Smith Apisarnthanarax: . . . so, I think the reason why . . .

Mika Sinanan: And the timing of that is beyond the harm questions that have been . . . that have shown up here.

Smith Apisarnthanarax: . . . for certain endpoints, like secondary cancers, yes. We don't need to analyze 30 to expose a kid unnecessarily to radiation to find out if they're going to get a cancer. That's where the ethical question comes into play. So, I think that's why you have to sometimes extrapolate what's not there and what's there. Right? So, even though we don't have, in the last five years, evidence that protons don't decrease secondary malignancies, we know historically that exposure to the heart causes heart problems. That's not debatable.

Mika Sinanan: So, my takeaway from those series of issues, which gets back to Chris's question is that while the biologic effect appears to be similar from the

studies that we've seen, at least not significantly different, the harm appears to be less. The harm may be underrepresented in the longterm in pediatric cases. There are very rare instances across all of these studies where the harm of the proton beam therapy is actually greater than other radiation modalities. Almost always, it's either the same or less. It may not be significant, but it's less, almost always. So, on the basis of those considerations, I don't see a reason to change our coverage policy for pediatric cases, because there's a substantial amount of that, that we don't know. These studies, I give the charge back to our colleagues and to all of the proton beam centers is, you really need to get this data. You need to do the registry studies, and you need to track these people down and figure this out, because that's our responsibility, but we don't have a basis, at this point, to say that there is substantially new information and from the analysis that I just went through, it seems to me that there is a, at least, benefit now and a potentially increasing benefit to reduction of harm in the longterm. That's my feeling about this, in the pediatric situation.

Kevin Walsh: Well, I want to go back to the point Tony made, which is, if there is, and this would have to be discussed in terms of adult cancers, but, I mean, to paraphrase you, or you can just say it again, if there was that much . . . if there's all this much benefit to protons versus photons, where's the evidence.

Mika Sinanan: Alright. So, let me paraphrase what I thought [inaudible], and you can agree, the dosimetry evidence would suggest that there is a very significant different in the surrounding tissues relative to the tumor. Much greater than we see in the data of apparent harm. Right?

Tony Yen: Because of, like, the dosimetry, like, the mapping that I saw, the tomograms or whatever you want to call it, I would think that we see, like, very little to any toxicity.

Mika Sinanan: We should see very little toxicity.

Tony Yen: That's what, at least the dosimetry mapping tells me, but then we still see toxicity. And I'm scratching my head as to why?

Mika Sinanan: Is that because those pictures are kind of ideal and, in fact, there is more overlap to healthy tissues in the normal situation?

Tony Yen: I don't know.

Mika Sinanan: Or is it because of the neutron back scatter?

Smith Apisarnthanarax: I'll speak to that. I wish . . .

Sheila Rege: [inaudible]

Smith Apisarnthanarax: I wish protons were maverick, but they're not. So, there's always some degree of radiation exposure, even with protons, as it goes in. Right? If the tumor is . . . if there's something touching the tumor, like, a brain. There's brain tissue next to a tumor, you're going to expose brain tissue. It's not magic, unfortunately. So, what it does is just substantially decrease the just overall exposure. So, I think you're still going to see toxicity. And I think as it was said before, it's not the question, it's the magnitude. As we all know, you may need hundreds of patients, maybe thousands of patients to really see what you need to see, and those studies maybe we just don't have enough patients, too much heterogeneity. So, everything just washes out. That could explain why we're not seeing exactly what we should be seeing.

Gregory Brown: Tony, remember, those pictures are models.

Tony Yen: I know.

Gregory Brown: They didn't measure that sort of radiation.

Tony Yen: I completely understand that.

Gregory Brown: It's purely theoretical, which, again, the physics are physics, but . . .

Tony Yen: Right.

Gregory Brown: . . . they are idealized.

Tony Yen: So, what I'm also trying to get at is . . .

Smith Apisarnthanarax: I have to, let me comment about that. It's true but not true. I mean, for every single patient that we plan, there's quality assurance with measuring the exact depth of where it's supposed to go before we treat a patient. So, I think that what we see on the computer it's not disputable. It's reality. It's not theoretical.

Tony Yen: I'm not debating any of that. What I'm trying to really kind of understand is that, the difference, that marked difference between the basic science and the clinical outcomes, and their true, true clinical differences. And I think that's the discrepancy that basic science would tell me that, wow. This is going to be the best thing since sliced bread. Or it's going to be a

marked clinical difference. What I see is some, but not as marked in either outcomes with either overall survival or progression free survival or toxicities. There are some differences. We've gone through the literature, but I just don't see that magnitude that I would expect from what the basic science is informing me about.

Kevin Walsh: That's the point I'm trying to respond to you, Mika, that your supposition . . . I don't find that your supposition about longterm . . . proposed longterm benefit to children is backed up by any of the studies of adult cancers that were being shown. So, I want to believe your supposition, but I am not . . . I don't see anything that tells me it's more than a supposition.

Seth Schwartz: One more comment, I guess, and maybe our vendor can speak to this a little bit, but, so the same thing we're talking about with the chondrosarcomas is, the patients that are getting protons are pretty selected already. So, we don't . . . we're not seeing a lot of randomized trial data. So, I'm curious, how fair the comparison we're really looking at. So, the other patient that you're worried electrons are going to lead to high toxicities, so you select and we say, we're going to give them protons to avoid these toxicities. And then, you compare the outcomes of toxicities between the group that got protons and the group that got photons, and they're about the same. Is that really a fair comparison when you've selected the patient that got protons in order not to get electrons. So, I'm . . . certainly in the retrospective data there's going to be some of that in there. We don't have a lot of randomized trial data. So, I am also struck by the fact that the differences are not nearly as large as it seems like they should be, but I'm just wondering if there's reasons why that's the case.

Smith Apisarnthanarax: I think I spoke for it. There's just patient selection, as you mentioned. There is heterogeneity of many factors that come into play, and particularly for pediatrics. We're talking about chondrosarcomas. This is a very rare tumor. You're not going to get any randomized data, period. So, you just have to do what we do in medicine is make your best clinical judgment.

Sheila Rege: One of the other things that we forget is in all these model simulations and stuff, you're assuming it's a fixed object. Our patients, they're moving. They're breathing. And you've actually got to be extra careful with protons, because it's more focused. We've gone a long way with imaging. We've gone a long way with breathing and control and all that. I tell my patients with prostate cancer, one of the things that you can't control when you pass gas and stuff and things move air. So, when Tony . . . when you're saying that the results are not as great, maybe they will be at some point, as technology catches up, but I do agree that with children, you

don't want any unintended consequences of dose scattered to a bone that's still developing.

Seth Schwartz: The other thing that strikes me is related to these toxicities, which tissues are likely to show the most immediate effects. So, it's going to be upper digestive tract. It's going to be obvious, right? You have xerostomia. You have all the pain. You have inability to eat, inability to swallow. When we look at those outcomes, and again this is more adult than it was in pediatrics, because we don't have any in the peds, it is pretty clear that there is a benefit, as far as toxicities. And that's the one area where the benefits were pretty clearly stated. It may be less clear in some of the other tissues where there's no very easy way to assess what the toxicity is. So, I don't know. Again, I don't know where that is, but it's, depending on which [inaudible] you're looking at, how evident the toxicities are may be a matter of a measurement issue.

Kevin Walsh: Weren't those benefits limited to neoadjuvant therapy for esophageal? I don't think they're generalized.

Seth Schwartz: Well, I was talking about head and neck more than esophageal. So, and I apologize, I don't know the data well enough to say for sure.

Gregory Brown: Usually, we need to go through our tool before we take a straw vote.

Josh Morse: Are you ready? Sure.

Gregory Brown: Anybody have any new comments or other things to say on peds? Since we're . . . OK. So, should we do page five? So, we've got safety outcomes. I guess for peds, we're talking about all, because that was the previous decision. Right? And so, I don't have any voting.

Sheila Rege: I have yours.

Gregory Brown: Oh. You have yours and mine, and you're recusing yourself. OK. So, again, part of this is comparators and there's . . . some were surgery, some were chemo. Some were just IMRT. Photon versus proton. There we go. So, I would say for the comparator here that we're concerned, is photon versus proton, the primary comparator? OK? Two different forms of radiation therapy. The safety outcomes there are listed. Endocrine related toxicities, other toxicities, white matter lesion, radiation necrosis, injury to central nervous system or brainstem, vascular hearing loss, neurocognitive enucleation, osteoradionecrosis. Any other safety outcomes there?

Sheila Rege: And for children, would you say, like bone growth, you know, kind of . . .

Gregory Brown: For peds?

Sheila Rege: Yeah. For peds.

Smith Apisarnthanarax: Asymmetry of bone growth.

Sheila Rege: Bone growth asymmetry.

Male: Did you see that in the study?

Sheila Rege: Oh, no. Actually, they were not on, no, but that's [inaudible].

Gregory Brown: OK. Any particular safety discussion or outcomes? So . . .

Josh Morse: And I'm not saying you can't list those . . .

Gregory Brown: . . . sure. Yeah.

Josh Morse: . . . what's [crosstalk].

Gregory Brown: We have no evidence to vote on.

Josh Morse: The process that I go through the information provided by the vendor [crosstalk], but you could add to this. It's yours.

Gregory Brown: So, again, the comparator is important. So, for safety, more in some would be saying that proton beam is safer than photon in some. OK? Less than some would be saying proton is less safe than photon. OK? So, vote on safety.

Tony Yen: I just have some. I don't have more.

Gregory Brown: I think that's the same.

Josh Morse: Some or more [crosstalk]. Christine, can you check for the cards while we're voting? Thanks. Chris, were you some or more?

Chris Hearne: More. [inaudible] OK. And Dr. Friedly is on the line. Dr. Friedly?

Janna Friedly: Can you hear me?

Gregory Brown: We need to turn the volume up.

Josh Morse: Can you turn the volume up on the phone, Christine or Chris?

Christine Masters: Dr. Friedly, are you on the phone?

Janna Friedly: I am on the phone. Hello?

Christine Masters: There we go. We heard you.

Janna Friedly: You can hear me?

Christine Masters: Yep.

Janna Friedly: OK. So, I just want to say I'm a little bit confused about the more and then some. So, are they the same thing?

Josh Morse: Yeah. They're close to being the same.

Gregory Brown: Well, it's more than some or less than some.

Janna Friedly: OK. That's my, more in some.

Josh Morse: OK. Then, 1 [inaudible] of 8 more in some.

Gregory Brown: OK. Efficacy. Oh, sorry?

Josh Morse: For pediatric [inaudible] and 8 more in some, 1 [inaudible]. Where is Chris? Thank you. There she is. Thank you. Did you get that Chris?

Christine Masters: Yes. I did.

Gregory Brown: Efficacy effectiveness, overall survival, progression free survival, mortality, distant metastases, local regional failure free survival.

Mika Sinanan: I have no equivalent.

Josh Morse: OK. So, we'll say three equivalent, one, two, three, four, five, six, so four equivalent, six more in some, and one recuse. Thank you.

Janna Friedly: And I was equivalent.

Josh Morse: Five equivalent. Thank you, Janna. Thanks. I have too many votes. So, I think it was five and five.

Gregory Brown: OK. And then, cost outcomes.

- Mika Sinanan: So, cost is higher? What is, OK. Got it.
- Gregory Brown: So, in the room, we have nine unproven and Dr. Friedly?
- Janna Friedly: Unproven.
- Josh Morse: So, that's ten and one recusal.
- Gregory Brown: And then, our, OK. So, are we ready to vote on peds then, I think? I'm taking a guess [inaudible]. Straw poll, or what, for peds. Just for peds. OK.
- Josh Morse: OK. So, in the room, there is one, two, three, four, five, six, eight cover. One cover with conditions, and Dr. Friedly is nine for cover. OK. Nine and one. OK. So, it's nine cover unconditionally and one cover with conditions. OK. Thank you. And one recuse. Correct.
- Gregory Brown: So, since we have nine cover, then we don't need to discuss conditions. Right? OK.
- Josh Morse: Final vote. So, cover for pediatric cancer. So, that's cover no conditions for pediatric cancers?
- Gregory Brown: Yeah. So, and this is more a process question. Is pediatric 18 and younger, or 21 and younger? Is there a . . .
- Mika Sinanan: 21 is what they said before, I thought.
- Gregory Brown: I'm asking, again.
- Josh Morse: Maybe Dr. Skelly can differentiate that?
- Andrea Skelly: Because of HCA and Medicaid, we usually consider kids to be less than 21 years of age. I don't see why we'd change that or try to do one HCA. So, I think that would be what we'd use, unless you tell us otherwise.
- Gregory Brown: I don't think there's enough evidence to differentiate between 21 and peds, so . . .
- Josh Morse: So, 21 is the [crosstalk] policy?
- Andrea Skelly: Less than 21.

- Gregory Brown: Less than 21. OK. OK. That was the fairly easy part. Now adults. Comments. Who wants to say what they're thinking?
- Tony Yen: I like Health Care Authority's recommendations, in terms of the coverage conditions. I would think about covering with conditions for adults, except the one thing that the evidence vendor presented is that perhaps esophageal cancer has an incremental benefit. That's the only thing I would amend with for what the HCA has recommended. I think it's on the, let's see . . .
- Kevin Walsh: Slide 21.
- Gregory Brown: Page 21, yeah, or slide 21, page 11 of the presentation. So, adult recommendation, cover with conditions if esophageal, liver, brain, ocular were the four that are listed.
- Seth Schwartz: If they were going to do that, I would add in head and neck and skull base to specify that from . . . I mean, brain and skull based is kind of left out. So, I would say skull base . . .
- Sheila Rege: Uh, would you . . .
- Seth Schwartz: . . . and head and neck.
- Sheila Rege: . . . add all head and neck or skull base with head and neck?
- Seth Schwartz: I would include all. I think we saw some of those differences there in terms of the toxicity differences in the head and neck tumors. That was compelling to me.
- Gregory Brown: So, esophageal, liver, brain, ocular, and head and neck?
- Christine Masters: Hold on.
- Gregory Brown: No, not to put it up, I'm just clarifying. So, those are the five then we're talking about?
- Seth Schwartz: As long as skull base is included in brain, I would call that.
- Kevin Walsh: What I am reading is cover with conditions.
- Gregory Brown: Well, again, we're just talking right now, so.

- Kevin Walsh: Right. I'm aware, but we're talking . . . so, do we want to go through each one and identify the conditions? Or do we want to . . . maybe we should get a straw poll to see if everybody agrees with that, or to know if we have to back up one step.
- Gregory Brown: OK. Well, I guess first of all the straw poll is, are most people leaning towards cover with conditions? OK. Everybody. Yep. OK. Dr. Friedly, are you on cover with conditions, as well?
- Janna Friedly: OK.
- Gregory Brown: So, we all agree. So, then I would suggest let's put what those proposed conditions are, and then we should probably talk about those conditions individually. Does that make sense? OK.
- Mika Sinanan: The one other area that has been raised, we didn't see data for it, was re-radiation.
- Janna Friedly: And also patients enrolled in a trial or registry. Where does that?
- Gregory Brown: Alright. So . . .
- Josh Morse: Can I comment on that? So, in the Medicaid rules, I believe under Uniform Medical Plan, as well, basically you don't need to address that.
- Gregory Brown: OK.
- Josh Morse: The question of if in a trial, because the agency has the authority to, if a person is in an appropriate trial to authorize that outside of your decision.
- Janna Friedly: OK. Thank you.
- Mika Sinanan: So, thank you. So, may I ask another question, since you raise that issue. Is there an option for, to be reviewed. In other words to request a review for special circumstances?
- Gregory Brown: So, if I understand right, they have the option to cover it, if there in an appropriate trial, but they're not required to cover it. Is that correct?
- Mika Sinanan: Yes. So, that's a . . . I understand that, but this is a separate question. They have a . . . Shiela has a patient who, for special circumstances, and we could imagine some of them, in another area where there is . . . where she has established that the risk of photons is excessive. Is part of our capability

here to say that there is an option for the Health Care Authority to do a review under special circumstances?

Gregory Brown: So, I will speak to the [crosstalk].

Seth Schwartz: Can I speak up for one second?

Gregory Brown: I see what you're saying. I think on your second slide where it said all agency . . . at agency discretion. And you said you preferred not to have that.

Seth Schwartz: But I think the question is, is there some verbiage that we can make to accommodate those situations that we envision them needing to review. So, I think one of the things we saw was, in other tumors if there are regional structures that would be at high risk, or something like that. There may be some terminology we can look at, but ultimately, that's what they're gonna, what you're asking them to do is determine that. If we can call that out here specifically, that would be better.

Mika Sinanan: Right. And the reason I raise that is because of the comment did you prefer not to, but preferring as opposed to it being a policy that . . . where there are special circumstances, there is a protocol or a mechanism for appealing.

Laurie Mischley: One of the other guidelines says tumors near organs at risk. That makes me feel much more comfortable. I feel like we do have a bird's eye view. And it makes me very nervous to take away this option from special circumstances.

Gregory Brown: So, what tumor doesn't have an organ near it?

Laurie Mischley: I like a little wiggle room.

Gregory Brown: I understand, but at the same time, is . . . I mean, again, this is not our decision, but just within the Unified Health Plan, is there some sort of an appeal for unique cases that, again . . . we can't . . . it's impossible to make a coverage decision to cover every scenario. It just will never happen. We can't envision them all. We can't . . . and every coverage decision with conditions would then have some of what we couldn't think of clause.

Seth Schwartz: So, Greg, I think what I'm struggling with is, there are some areas where we haven't seen great data on, on it being more effective than traditional therapy. We're not seeing great data to say that it's more toxic, or that it's significantly less toxic, but again, I think part of the reason for that, at least the way I'm reading this data is that it's because it's selected data. So, I'm

concerned about that element of it. I think ultimately, our concern is that if we cover this unconditionally, we're worried that there's going to be an explosion of people using this technology inappropriately. So, please let me finish . . .

Gregory Brown: OK.

Seth Schwartz: . . . so, I think that's our ultimate concern. So, what we want . . . I'm not inclined to restrict this egregiously, because it seems to me that at least in the right places, there are mechanisms in place to limit this appropriately and to use it appropriately when there are other organ systems or things that would be at undue high risk. We're hearing that there's this five system review. I don't know that all the centers operate that way, but clearly, there are some safeguards in place to be using this appropriately now. Or, at least that's the way I'm reading the situation. I don't know exactly what the verbiage looks like, but I feel like we should be able to construct this in such a way that there is the room to assess those patients and use this appropriately, as opposed to restricting it unnecessarily. So, that's kind of where I'm falling out. Again, people may have differences of opinion, but that's where I'm falling out on things. And if . . .

Gregory Brown: So . . .

Seth Schwartz: . . . we try to restrict it too much, I'm going to be leaning more towards cover unconditionally.

Gregory Brown: . . . so, I guess, I'll give you my personal response. That is, I think it was Dr. Zang that said they wanted a request for left sided breast cancer. I mean, if I remember my statistics right, the estimate is one in nine women will have breast cancer in their lifetime. So, it is one of the most common cancers in the world. I don't know any propensity of left versus right. So, presumably half of those are left sided. So, if we're saying that we have the associate medical director of this facility thinking that left sided breast cancer is an appropriate treatment but no evidence to support this, and there is a review of 600,000 patients with breast cancer showing no difference in outcome, I don't want them to have that option, even if they think it's the right idea. So, I'm very concerned about covering without conditions in that sense. I can see rare tumors that nobody knows what the right treatment is and nobody . . . there isn't sufficient data. As you say, you just have to do your best clinical judgment and I think that . . . but again, to me, the evidence for prostate is not compelling, but if we cover it for all, then they can start ordering it for prostate cancer. So, I don't know how to do what you're asking without opening it up for everything. I have a problem with that.

Smith Apisarnthanarax: We deal with this a lot in terms of insurance companies. In the category special circumstances, there are special circumstances that apply broadly to multiple diseases, like left sided breast cancer is very disease site specific, but an example would be re-radiation. Right? That's a special circumstance that is broad, but it's very specific that could be still applied broadly. Another example is if you're developing an IMRT plan and you just cannot meet your dose constraints safely, it doesn't matter what it is, then that's another sort of a broad category that's special. So, that could be one compromise of not just leaving it open to everything, but having some guidance in terms of what kinds of special circumstances, in general, could be considered. That's just one thought.

Sheila Rege: I have a question, though, for the agency directors. If somebody calls, and it's not listed in our criteria, do you have the latitude to look at it and say, this is really unusual and approve it, or not?

Female: It varies a little bit between programs. So, Medicaid has something called an exception to rule process where nothing is absolute and everything can be brought back, essentially, for a medical necessity review. That is less true on the employee and retiree benefits side of the house, in general. I think if you make a statement, it's going to be followed pretty much, as written. So, I would say, in general, if there's, like, if there's a type of category that you want to create, as an exception, if you can frame out that category, that's very helpful.

Sheila Rege: And general response to the dosimetry, and we at [inaudible] suddenly got asked, because there was a center that, not in the States, that just had really bad plans. Then, they tried to say, well, we want this, because your dosimetrist can make a plan look really bad if they don't want to do it. That's kind of the . . . there's no safeguard, because they're not going to know . . . they should have been able to protect that. So, that's the pull and tug we've then have to kind of protect against. I don't know how to kind of address that concern with that.

Seth Schwartz: So, something kind of equivalent. So, what I'm struggling with is, is again radiation, it's a tool. Right? And it's not . . . I'm a surgeon, so I'm thinking surgical equivalence, but essentially we covered, we looked at this situation. We looked at robotic surgery, and this came up, which is what we essentially said. We re-saw data on a lot of situations where a robot wasn't that different than other things and few situations where it was better, but we didn't feel comfortable as a group saying, we don't want to restrict the use of robotic surgery. We don't necessarily want to pay more for it, but we can't figure out a way to say that this shouldn't be used. It

should be at the discretion of the surgical teams and the hospitals decide who wants to buy a 2 million dollar robot and go from there. So, we covered it unconditionally. So, there's some parallels with this. I think I worry, too, about . . . I don't want 300,000 breast cancers being treated with protons. I think that's inappropriate, but . . . and I think maybe there's some ways we can constrain this so that we don't just simply say cover unconditionally, but to some degree, it seems like this is a modality that is at least in my opinion, equally safe and equally effective, and probably in some circumstances where it's more of both. And I don't know exactly how to restrict that. So, I mean, I think we can try to sculpt this language to do so, and . . .

Kevin Walsh: Go ahead.

Gregory Brown: No. I was just going to say, I mean, I think we can specify where there is evidence to support it. Then, I think one of them . . . one of the others said where other cancer treatments have already been tried or contraindicated. So, all other treatments have been tried or contraindicated.

Seth Schwartz: Exactly.

Gregory Brown: So, that should cover re-radiation. 'Cuz you can't radiate again. That should cover where tumors, they've tried everything else. So, this is the only thing left. So, is that enough of a . . .

Seth Schwartz: That's exactly what I'm talking about. I think there is some way that we can construct language that is sufficiently limited that not everyone is gonna get it and yet provides the opportunity at the discretion of the cancer treating teams, to figure out whether this is the proper modality for these patients. That's what I'm trying to . . .

Gregory Brown: OK.

Kevin Walsh: I want to go back to the analogy that you made. At the time, robotic surgery was not being paid for at a different rate than regular surgery. So, we felt comfortable not putting any conditions on that decision, because the economic . . . there was no economic benefit to doing one therapy over another. We know that the cost is at least 50% higher right now. And we don't know where it's going. So, it's not an analogous situation. There is a cost . . . there is a financial benefit to doing one therapy over another.

Josh Morse: Just for the record, I'm looking at, so robotic assisted surgery is a covered benefit with conditions. You made conditional coverage.

Smith Apisarnthanarax: So, I'm not in the financial part . . .

Gregory Brown: There is a differential payment here, too, for proton beam versus photon.

Smith Apisarnthanarax: I'm not privy to all the what goes on in the financial, but I'm getting a lot of shaking heads from the financial team over there. So, I'm not sure what that means, that it's not as expensive as . . . twice as much? Oh.

Gregory Brown: Actually, you're not, so.

Smith Apisarnthanarax: But, I guess that is possibly not 100% true. I guess it depends.

Gregory Brown: Again, we can only rule on coverage. We can't make payment decisions.

Smith Apisarnthanarax: Yeah.

Gregory Brown: So, that's irrelevant to us. I mean, it, again, I don't think there would be the problem here if the payment for proton beam was the same as photon radiation. So, then it would be just leave it to the clinicians to see what's best in each case, because there's no cost differential. It's as soon as that cost differential was introduced, there is now financial incentives to pick one treatment over another that are not clinically based. So, but again, we as a committee are unable to address those. So, we simply need to say, based on the evidence, what . . . if we're leaning towards cover with conditions, which is what the straw poll said, what are those conditions. So, again, if we can step back, I would say . . . can we see the, oh. I guess we do want to know what the cost is.

Female: I think there are two really key points to make. I think the first one is that our physicians aren't employed by us, and our physicians have no monetary reason to select protons over photons. Meaning, they get paid the same no matter what. So, when they're selecting protons over photons, it's because it is a superior [inaudible], and that's why we have so many selection criteria placed. Our reimbursement from a Regence perspective, so you can see, [inaudible] contact with Regence, and we believe it's very, very similar to IMRT. So, there really isn't a huge cost differential [inaudible].

Chris Hearne: Can you say the numbers on that, or just it's very, very similar?

Female: It's just very similar.

Chris Hearne: Oh, OK. Thank you.

Female: I'm sure we could pull the numbers for you. And we can certainly help provide those things.

Chris Hearne: And this is specific . . .

Gregory Brown: Most of the insurance contracts are proprietary and can't be disclosed.

Smith Apisarnthanarax: Right. So, I think the important thing is, I think when people hear those numbers, it could be true from many parts of the country, but specific to this proton center, because we're the only one in the state of Washington, they're saying that it's very similar. So, I don't know if that effects.

Gregory Brown: Well, again, it doesn't, because we don't make . . . that's an insurance negotiation issue. We're just . . .

Seth Schwartz: But I don't think that's fair.

Gregory Brown: . . . [crosstalk] on this.

Seth Schwartz: But I don't think that's fair either to say it doesn't, because we're deciding for the state of Washington. And if we're deciding based on three things, which is safety, effectiveness, and cost, and we have two of them are equivalent or better, whatever, and cost is the only thing that matters and our reluctance to approve this is that the cost is a driver, that it's twice as expensive, but if that's not the case, that's a valuable thing to know. Again, I don't trust that cost data, but I'm just saying, I think it's even more equivalent. It's not, like, I don't think we can simply say offhand that this is twice as expensive. So, I think we have to really downplay the cost issue, even though I think that is really the main concern after going through all of this.

Gregory Brown: OK. So, the . . .

Female: [inaudible]

Gregory Brown: . . . well, I just . . .

Smith Apisarnthanarax: The coverages are not the same as 521.

Gregory Brown: . . . right. No. No. No. I know. Those are down below. That's what I'm . . . so, yeah. So . . .

Female: . . . [inaudible] references to the other slide.

- Gregory Brown: . . . right. So . . .
- Female: [inaudible]
- Gregory Brown: . . . right. So, we added head and neck. So, the fifth [inaudible] head and neck? And I guess we're saying cancer or tumor on all these? OK. And . . .
- Sheila Rege: Was our evidence on liver, is that liver or liver mets? Are we doing liver primary, like, HCC?
- Gregory Brown: I think it's both.
- Mika Sinanan: There was very little evidence on mets, and it didn't give . . .
- Sheila Rege: Well, I was talking about liver HCC, but . . .
- Gregory Brown: Primary liver?
- Sheila Rege: Yeah. HCC is where I was seeing the evidence, but . . .
- Gregory Brown: So, after liver, if you want to put hepatocellular carcinoma.
- Kevin Walsh: Seth, I'm looking at the head and neck data in your slides, like, 66 through 72. Can you show me the benefits that persuaded you to add that?
- Gregory Brown: Can I just . . . and then, can we put one more?
- Sheila Rege: Base of skull chondrosarcoma and chordomas.
- Gregory Brown: Well, isn't that head and neck?
- Sheila Rege: With base of skull chordoma and chondrosarcoma be considered head and neck, Seth? It's not usually. It's usually called out.
- Gregory Brown: OK. Base of skull. So, yeah. I think it's the equivalency, as far as the outcome data. Then, if you look at the [inaudible] on the next slide.
- Kevin Walsh: Which slide are you looking at? I'm sorry?
- Seth Schwartz: On 63 with the mucositis data, dyschesia data, grade 3 toxicity and events. I mean, I think there's some compelling stuff in there that shows improved

. . . that shows lower toxicity profiles in the short-term with equivalent outcomes.

Laurie Mischley: And I kept hearing the vendor say, while not statistically significant, it may be clinically significant. And I heard several experts say that they were observing clinical significance, in their opinion. So, I know that the strength of evidence for an expert opinion isn't the same as a review, but I also do consider it legitimate, valuable evidence. And I don't think it serves us to invite experts and disregard their expertise.

Mika Sinanan: Jim, can I ask you, are we right not to be enthusiastic about prostate treatment with this modality? Because the data that we've got that I'm looking at seems to suggest pretty much the same path as the head and neck in the sense that there is not a whole lot of benefit therapeutically, but there's a decrease in certain types of side effect. Yet, prostate hasn't been on the window.

Smith Apisarnthanarax: Yeah. I think the data for prostate is fair in terms of reassessment. I think that's why there's an ongoing randomized trial right now that hopefully will give us the answer, but I think the data are too conflicting to really say one way or the other.

Kevin Walsh: Can you show me what you're looking at?

Mika Sinanan: I was looking at slide 99, which is sort of a summary slide on prostate. I was looking at the previous data that was more specific, but it seems like no significant differences between groups is the theme. Yet on slide 94, if you can see it, there's a suggestion. I'm not advocating for prostate. I'm simply trying to settle this in my own mind. There's a suggestion on slide 94 that toxicity is slightly less. Whether there's a significance there, I don't know. It's just the picture, the images that I'm looking at. So, if it's true that there's no significant difference between the therapies, what we've heard is that it's going to be a therapeutic decision made by the physicians on the basis not of any kind of [inaudible] certainly, and maybe not even on the basis of any economic practice that the physicians are going to decide on a treatment modality that is appropriate for the case.

Smith Apisarnthanarax: I think outside of rare circumstances, like re-radiation or a patient with severe inflammatory bowel disease, or something like that, I think the data is . . . what's out there is just not good enough to be said. If . . .

Mika Sinanan: But not to reinvestigate the pediatric issue, what we sort of said was that one of the facts is that we were interested in was the longterm toxicity that's only going to be manifest, perhaps, 20, 30, 50 years out. So, we

prepare to accept basic common sense and basics of physical principles, this idea the toxicity to adjacent tissues is important. We accepted that there. Is there any suggestion at all that in the prostate the same isn't true?

Smith Apisarnthanarax: Well, I think that's kind of Seth's point. I think, if you want to make certain subcategories with special circumstances, whether you're 20 or 21 or 22, it's just arbitrary. Right? So, whether you're 30 and you've got cancer, and you're going to be around for 30 years, the risk of secondary malignancy is relevant. So, a patient that . . . a prostate patient who refuses everything but radiation, and they're 40, reduction secondary [inaudible] is something that we talk about to patients, but that, I think, falls into a special circumstance, not for all prostate. So, I think that would be another category that I would sometimes consider for patients. If they're really young, and if they're gonna be around for a while, and so anything we can do to minimize radiation exposure is something that we think about.

Kevin Walsh: I don't see what you see, but also, I'm not comfortable with making a decision based on suppositions, which is what I think we're doing.

Mika Sinanan: The supposition being that there's a future benefit that we can't see?

Kevin Walsh: Yeah. And we can't see it in the data that we're given, but based on . . . if we go back to basic principles, then we can imagine that. I won't support that.

Gregory Brown: So, we had one other category we talked about, other tumors with completed . . .

Mika Sinanan: No other reasonable . . .

Gregory Brown: . . . with no other treatment options.

Mika Sinanan: . . . or acceptable treatment options.

Gregory Brown: No, no other treatment options or, yeah, contraindications.

Sheila Rege: Or other treatment options are contraindicated. Is that too broad?

Gregory Brown: I don't think so. That's out of your radiation field. You can't do conventional photon radiation . . . so you need to radiate with photon beam? Or you've done your chemo, you've done surgery, it's next to a

vital structure, but contraindicates proton therapy. Do we need to say tried or just contra-, I mean, to me the contraindication would be enough.

Chris Hearne: That can get interpreted in a lot of ways. Then, it gets back to the question, how granular we want to be in . . . because somebody might look at, for example, take the example of left sided breast cancer and say, well, there's going to be radiation to the heart. So, I think that's contraindicated, and they're going to . . . for example, that may be interpreted that way.

Gregory Brown: So, there's chemotherapy. There is surgery. There is . . .

Chris Hearne: Yeah.

Gregory Brown: . . . lumpectomies. I mean, there's all sorts of treatments. So, where all other treatment options are contraindicated.

Seth Schwartz: And add in the all. I think you should add in the all.

Gregory Brown: Again, ultimately everything we do is subjective. I mean, we're subjective in how we made a diagnosis, you know? So, anyway . . .

John Bramhall: So, on that last . . . not to be extremely inferior about it, but the situation then with that last parameter, is the physician is going to say to the patient, we would like to do photon therapy, but we can't, because when we analyze you there, we're going to give you too much toxicity to your other tissues. So, we'll try and get an exemption to do photon therapy. And if the next sentence then, is the next sentence, it won't be as good, but it's all we can do?

Smith Apisarnthanarax: Another way would be just to add verbiage about safety. I mean, that is subjective, but it's better than just contraindicating.

John Bramhall: Right, but that sentence, it won't be as good. The proton therapy isn't as good for your treatment. We would rather do photon therapy, but we can't. Therefore, we'll do proton. Is that a, I mean, is that a likely sentence that the physician would use? Or would they say, it's exactly the same in outcome, benefits, or it's just as good. So, we're not losing anything here.

Gregory Brown: So, again, just in our context in this state, if there is, OK. If there is one facility in the state doing it, and they have a multidisciplinary board that is reviewing tumor cases in patients and treatments, you're essentially saying that entire team is going to say everything else is contraindicated. We agree.

- John Bramhall: No. I'm not saying that at all. I'm saying, this . . .
- Gregory Brown: No, but that's . . .
- John Bramhall: . . . I, I, I'm not . . .
- Gregory Brown: . . . the pragmatic, no. I'm just saying, but that's . . . we're in Washington. There's one facility.
- John Bramhall: Right.
- Gregory Brown: And that facility has this process.
- John Bramhall: Look, I'm not arguing your motive. I'm asking the question whether the proton therapy for that tumor, whether there would be many circumstances where, in fact, you didn't want to do proton beam therapy. You didn't want to do that at all. And what would those circumstances be, because what we see is either equivalence or slight benefit. We don't see a lot of places in the data where the proton beam is harmful or is not as effective at killing the tissue at hand. So . . .
- Smith Apisarnthanarax: So, you're basically asking, what scenarios would we not want to use protons. Is that what you're asking?
- John Bramhall: Sort of, but that's [crosstalk] answer to that, but.
- Smith Apisarnthanarax: So, but that's related to this, uh, indication or I'm not really sure I understand.
- Gregory Brown: I'm missing something, John.
- John Bramhall: So, tumor X, you can't treat because there's too much damage to surrounding tissues. Therefore, we're going to claim an exemption and appeal and get funding for photon therapy. My question is, is the next sentence to the patient, the proton therapy won't be as good for tumor X. That's why we didn't use it in the first place. That's why we wanted to use photon therapy.
- Smith Apisarnthanarax: I think that's hard to make that determination in what was done [crosstalk].

Gregory Brown: I mean, again, to me, what we're trying to do is prevent gaming the system. And the scenario . . . I don't understand the scenario that you're trying to describe. You know, in other words, is there a back way for someone to get [crosstalk].

John Bramhall: No. Not I'm even suggesting nefarious intent. I'm not going there. I'm not . . .

Gregory Brown: Yep.

John Bramhall: . . . I'm not thinking of gaming the system or filling out the patient list for the scanner that's half empty. I'm not going there. I'm trying to find out, in my own mind, where the . . . and I know there's a whole thousand range of tumors that you could look at, but in principle, here what we're saying is that we would like an exemption for a tumor that we would like to do photon therapy for, but we can't. Therefore, we'll do proton. Are there good examples of that kind of tumor?

Mika Sinanan: I think it's your statement that is confusing, because normally you wouldn't say, I'd like to but I can't. You'd say, the best option for you, given your prior treatment, is protons. And we're going to make an application for it. It's not 100%, but the reason for it is, you've had this previous treatment. If we try other alternatives, you're going to have . . . you already had this chemotherapy and you had adverse toxicity, you had photons already. We can't give you more of a radiation dose. The only way we can give you more radiation safely is by using a different targeting technique, which is photons . . . or protons. I think that's the way it would go.

John Bramhall: That's quite right, but then the question that you might have is, well, why didn't we pick proton in the first place? What was the reason for not picking proton in the first place?

Smith Apisarnthanarax: I don't think that plays a role.

Mika Sinanan: We have that argument all the time with expensive versus generic drugs and so on. All we do is say, as far as I know, it's equal. It's just a lot less expensive. We're all about cost efficiency, because it's your tax dollars.

John Bramhall: So, in the back of my mind is that there may be an economic component to the decision, that it's not purely a therapeutic intervention effectiveness, it's an economic issue.

Smith Apisarnthanarax: Right, but I think it very well could be that we agree with photons in the first place, but now we're dealt with a new scenario where protons now is

appropriate when it was fine, IMRT was fine before, but that's . . . I don't think that should play a role into this particular scenario that we're dealt with.

Gregory Brown: It's not just photon, but it is chemo. It is surgery. It is, you know, every other treatment. So, if you've got too much cardiac toxicity from your previous chemo, you can't do chemo anymore. So, you're worried about heart toxicity from photon treatment. So, you do protons. So, I mean I . . .

Sheila Rege: So, looking at that, I think, first all of them are fine. When you say other tumors where all other treatment options are contraindicated, I almost wonder if we should say recurrent tumors. That's when we struggle with doing good dose distribution with photons. I think that's how this all started, re-irradiation. So, you're not going to [crosstalk] . . .

Smith Apisarnthanarax: I guess my comment to that is, and again, we can come out with a million different scenarios. Right? I think there are circumstances where a cancer is not recurrent, and there are special circumstances. For example, if a patient had prior history of Adriamycin and had fulminant pulmonary toxicity where they almost died.

Sheila Rege: Recurrent tumor.

Smith Apisarnthanarax: No. No. No. For something else, like maybe a lymphoma. Right now, they have a lung cancer. That's a different kind of cancer, not recurrent.

Sheila Rege: Recurrent or second cancers or something, because that's where . . . and I know I argue with the Medicaid director on a lot of other stuff, but if you open this up, I can make a case that in my mind I want protons for my patient for anything, and I think it's co-, anything else is contraindicated. So, this is . . . my interpretation is that's a blanket statement that can be used, but if that's what the committee wants, as a radio-oncologist, I could make an argument for anybody if I really believed in protons for everything.

Smith Apisarnthanarax: If we were just talking about, say, Washington, I guess you're going to have to . . .

Sheila Rege: Or maybe tomorrow there'll be [crosstalk].

Smith Apisarnthanarax: I think that's fair. I think that's fair, but . . .

Sheila Rege: Because [crosstalk].

Smith Apisarnthanarax: . . . but I think that then it goes back to the discussion of how restrictive or broad you want to be, because I can think of many scenarios where for various reasons, and it may not be a secondary cancer, but there is a cardiac extremely poor cardiopulmonary morbidity. Even just sitting on a lung with radiation is gonna be very dangerous. So . . .

Sheila Rege: But people don't [crosstalk] with proton [crosstalk].

Seth Schwartz: Can I take a different tactic? What about, I mean, I think while we're feeling comfortable, well, at least I'm feeling a little bit more comfortable with our current scenario, is that we understand there is a multidisciplinary group that's reviewing it. So, what about simply saying that? Saying other tumors if a multidisciplinary group determines that it's the best modality. I mean, I don't know exactly what . . . we can figure out the wording, but just taking that path rather than saying everything else has failed. Instead saying, not just one physician says I'm going to do it, but if a multidisciplinary tumor panel says this is the best treatment option for this patient, I mean, that seems . . . that's what I want. Hearing all this data, because I'm thinking about, again, we can talk about all the [inaudible] we want, but if it's . . . say it's a 23-year-old woman with left sided breast cancer who has already had an MI for some childhood thingamajig, and I want to be able to offer that woman protons, or at least if her cancer team decides that's the best way to care for that patient, I don't want to restrict that and say, sorry. Can't get it. That doesn't make sense to me. So, I do want to leave some wiggle room for an appropriate body to be able to review this. Again, I don't know exactly what the language is, but that would be maybe the reverse path from this, restrictive . . . so it's restrictive, but not based on specific language.

Gregory Brown: I would say multidisciplinary board and . . .

Mika Sinanan: Other treatment options reviewed by a multidisciplinary board.

Sheila Rege: Well, are contraindicated based on review by a multidisciplinary board. No?

Mika Sinanan: Contraindicated.

Smith Apisarnthanarax: Other tumors where all other treatment options are contraindicated.

Sheila Rege: Yeah, are contraindicated. That doesn't make sense.

Gregory Brown: After review by a multidisciplinary [crosstalk].

- Sheila Rege: Other treatment options are contraindicated after review by a multidisciplinary. Then, that makes sense. Otherwise, you just change it to all other tumors via multidisciplinary board. Either . . . whichever way you want. Are contraindicated.
- Gregory Brown: After options, yep, are contraindicated. After, and then just change reviewed to review by a multidisciplinary tumor board.
- Sheila Rege: Yeah. I like that Seth.
- Gregory Brown: So, it's codifying what currently exists, but if a new facility comes in, and they set up a multidisciplinary board, then they can do it, too. OK?
- Teresa: This is Teresa from the Health Care Authority. I'm thinking about implementing this. Can you . . . is it possible to be more specific, as to what multidisciplinary means or what you're hoping to have that group provide, because someone could say, well, I have a podiatrist. I have a cardiologist. I have a cancer doctor, which would be multidisciplinary. So, it would be helpful from an implementation perspective if we could get a little more granularity.
- Sheila Rege: We could say [inaudible], or, like a tumor conference is what we're talking about.
- Seth Schwartz: Representation by surgery, radiation oncology, and oncology.
- Smith Apisarnthanarax: [inaudible] from a tumor board, you're not going to have a cardiologist just there, or a podiatrist.
- Sheila Rege: Yeah. [inaudible] tumor board is considered, there are standards, but we could say it's . . .
- Teresa: My apologies. I didn't see tumor. Tumor wasn't up there when I turned around to talk. So, I apologize.
- Gregory Brown: Space. Space. Definitely space. [crosstalk]
- Josh Morse: So, this is what you would cover. Is there anything that you would not cover based on the evidence that you reviewed?
- Gregory Brown: Well . . .

- Mika Sinanan: So, are you asking within these categories, because there's a line that's missing off there that says all other treatment is not covered. At least it used to be there.
- John Bramhall: And treatment for things like AVM's is not, it's part of the possible scope here, but . . .
- Sheila Rege: Would AVM be considered a benign tumor and be covered after review by multidisciplinary board?
- Male: So, AVM as a [crosstalk].
- Sheila Rege: Benign tumor.
- Male: Alright.
- Emily: Just within this scope of the literature review [inaudible].
- Gregory Brown: So, there again, for AVM to be covered, you'd have to say embolization from neuroradiology or surgery or contraindicated.
- Andrea Skelly: Can I just take a point of clarification in terms of the list. For the purposes of the report, which are given . . . and your purposes, head and neck included skull based, as well as non skull based. I don't know if that matters to your list here.
- Sheila Rege: Yeah. We were going to do base of skull chordomas and chondrosarcomas, and you consider that head and neck?
- Andrea Skelly: That's where we put it, but we noticed that the skull base was there [crosstalk].
- Seth Schwartz: I think they're viewed differently from a medical perspective. Typically, head and neck cancer refers to squamous cell carcinomas and other salivary gland tumors of the head and neck, and skull based tumors are a different [crosstalk].
- Andrea Skelly: I'm just trying to be complete.
- Sheila Rege: [crosstalk] skull base tumors or base of the skull chordomas or what . . . how do you . . .
- Seth Schwartz: I would say skull based tumors. I don't think you need to be that specific.

- Sheila Rege: Skull based tumors? Skull based tumors would come under brain.
- Seth Schwartz: And I guess the only, and I don't know if this is a question, but there's benign and malignant skull based tumors. So, I think it's . . . whenever I say skull based tumors, because we're referring to cancer here, and you're talking about sites for everything else, just say skull base.
- Gregory Brown: We should have tumors after everything, obviously. I would leave it.
- Sheila Rege: It's [crosstalk] cancers.
- Seth Schwartz: Well, think all the others are cancer, whereas a lot . . . many of the skull based lesions are benign lesions and we'll still use stereotactic radiosurgery or gamma knife, but usually . . . but protons are usually not at play. It's probably not going to come up, but I don't know that it . . . but it might make sense to say skull based cancers.
- Sheila Rege: So, we would say esophageal cancers. Spinal may be tumors. Right?
- Seth Schwartz: Is there any circumstance for using this for benign?
- Female: No.
- Sheila Rege: [crosstalk] cancers. Right?
- Seth Schwartz: I think this is . . . I mean, all the data we looked at was cancer.
- Sheila Rege: Spinal cancer.
- Seth Schwartz: You could just put at the top to say covered for the following cancers. Then say, I think . . . I mean, there's zero evidence for using protons for nonmalignant disease.
- Gregory Brown: [crosstalk] cancer. Is that what you're saying?
- Sheila Rege: Well, but then you've got tumors in there, too, with other . . .
- Seth Schwartz: Yeah, but what I'm saying is just at the top have a sentence that says covered for the following cancers, and then you list by site. And then, at the bottom say not covered, all other cancers.
- Sheila Rege: But then you've got ocular could be a melanoma, not a cancer.
- Seth Schwartz: Melanoma is a cancer.

- Gregory Brown: Not carcinoma [crosstalk].
- Sheila Rege: Other tumors, AVMs, we're trying to cover AVMs.
- Seth Schwartz: Are we trying to cover AVMs? I don't . . . I mean, I don't think I saw any data on AVMs. So, I mean, I . . . what's [inaudible] here is that I think is that at least we're to stick to the data that we've seen. Right? Which we haven't seen great data for everything, but we saw zero data on AVMs. I think we heard someone mention it, but that's a little bit of a different story. So, if we're going to use this for benign disease, I'd like to see some data on that. Whereas, I think the advantage of using this for cancer is that we're seeing data that is at least equivalent in the majority of circumstances, and the toxicities are better, but I don't . . . we don't want to broaden this. Otherwise, just cover it. Right? So, I think we're trying to keep this sufficiently restrictive, but we don't want to open it up too much. I don't see any evidence for any benign disease.
- Sheila Rege: So, then, we need to then remove . . .
- Gregory Brown: Well, we should have skull based cancers.
- Sheila Rege: OK, but then . . .
- Female: [inaudible]
- Sheila Rege: . . . no. He doesn't want tumors.
- Seth Schwartz: Well, I mean, I don't want to dominate the discussion here. I'm just saying, if anyone feels strongly, wants to include tumors, I'm not . . .
- Gregory Brown: No. I think you're right. I mean . . .
- Sheila Rege: [crosstalk] cancers. And then, did we remove the tumors from there? Others . . . [crosstalk].
- Female: [inaudible]
- Male: Take it out.
- Mika Sinanan: Other cancers.
- Sheila Rege: Then, not covered, all other . . .

- Gregory Brown: All other cancers.
- Sheila Rege: We leave tumor out of the tumor board.
- Emily: I would just say, if you say not covered for all the other cancers, then you left no decision around benign causes. So, if you say not covered for all other conditions, then you've said it will be covered for those.
- Sheila Rege: Did we have them 2014.
- Chris Hearne: I don't think so. Central nervous system.
- Smith Apisarnthanarax: So, if it's re-radiation of an AVM, that's not a cancer, but if the brain has already got radiation . . .
- Sheila Rege: We'll hear.
- Seth Schwartz: That's a special enough circumstance that we could leave that one out maybe.
- Sheila Rege: Yeah.
- Female: Real quickly, the prior report included six case series on AVM and concluded it was insufficient. We found no new studies at all in AVM.
- Gregory Brown: Is contraindicated got a blue line, because it's wants a hyphen in there between contra . . .
- Female: [inaudible].
- Gregory Brown: Huh?
- Female: [inaudible].
- Gregory Brown: Well, so we've actually kind of . . . we said we were going to put a list up and then talk about them one at a time, but does anybody want to talk about any of them individually? I guess I'm not seeing anybody saying yes they want to talk about it individually. OK. So, we've got a recommendation. We haven't even gone through our tool yet. So, I would say, let's go back to our tool. Now, we did peds, and now we're doing adults. This was page 5.
- Female: I'm sorry. Can you just interrupt for one sec. This is [inaudible]. I just want to make sure I'm thinking about how this will be implemented. Just

confirming that the intended language that liver would be only for hepatocellular carcinoma and not for liver mets.

Male: I think so.

Female: OK.

Gregory Brown: Sufficient evidence regarding mets. Was there any evidence on mets?

Mika Sinanan: There was one study that showed a few cases, insufficient.

Gregory Brown: OK. So, we've already gone through the safety concerns and anybody want to change anything, comments? Or are we ready to vote in safety? So, we need to go to our tool first. Safety. More and some?

Josh Morse: Nine more in some in the room.

Gregory Brown: Dr. Friedly?

Josh Morse: Dr. Friedly?

Gregory Brown: I had a beep.

Janna Friedly: More in some.

Gregory Brown: More in some. OK. So, ten . . .

Sheila Rege: And one abstain.

Josh Morse: OK. Thank you.

Gregory Brown: OK. Then efficacy.

Janna Friedly: More in some for me.

Josh Morse: OK. Six, is that right, more in some? Six more in some. Yeah. One, two, three equivalent.

Gregory Brown: No, seven. Dr. Friedly said [crosstalk].

Josh Morse: Seven, sorry.

Gregory Brown: Seven, three, and one recuse. Then, on cost.

- Josh Morse: OK. Eight unproven, one more in all . . .
- Gregory Brown: Dr. Friedly?
- Josh Morse: . . . Dr. Friedly?
- Janna Friedly: Unproven.
- Josh Morse: Nine unproven, one recused.
- Gregory Brown: We had agreed before, we're going to take a break just to let the agency directors look at this, make sure there isn't any spelling or things that they're thinking of, just kind of walk away for a second. We'll reconvene in five minutes?
- Josh Morse: Sounds good.
- Gregory Brown: OK.
- Josh Morse: Thank you.
- Gregory Brown: OK. So, we had one comment from the agency directors about hepatocellular carcinoma. They wanted to make sure that it was not metastatic hepatocellular carcinoma somewhere else. Initial suggestion was hepatocellular carcinoma of the liver. And I just said, how about primary hepatocellular carcinoma? That will take care of the metastatic issue. It doesn't sound awkward . . . quite as awkward to me, anyway. OK. Any other thoughts, comments before we are ready to vote? OK. Dr. Friedly are you . . .
- Janna Friedly: I'm here, would you mind just reading the wording so that I can . . . because I can't see the [crosstalk].
- Gregory Brown: Chris can you lower that just a second? Just so I can read it to Dr. Friedly. Covered for the following cancers: Esophageal, head/neck, skull based, primary hepatocellular carcinoma, brain/spinal, ocular, other cancers where all other treatment options are contraindicated after review by a multidisciplinary tumor board, not covered-all other conditions.
- Janna Friedly: OK. Thank you.
- Gregory Brown: So, I think we are unanimous on cover with conditions, except for one recusal. And your vote?

- Janna Friedly: Yes. I approve.
- Josh Morse: Cover with conditions?
- Janna Friedly: Yes.
- Josh Morse: OK. That's ten cover with conditions and one recuse for adult treatment cancers. Thank you.
- Gregory Brown: OK.
- Josh Morse: One final thing. I'm sorry I didn't mention this earlier. We are contemplating moving the November 15<sup>th</sup> meeting of 2019 to November 22<sup>nd</sup>. So, we will send you an email asking if you can check your calendars about that. That would be the Friday before the week of Thanksgiving. We would be moving it one week later into November, just for this one time. So, we will follow up with you with a note by email.
- Female: 22<sup>nd</sup> to 29<sup>th</sup> or?
- Josh Morse: 15<sup>th</sup> to 22<sup>nd</sup>. We need to check the Medicare. I'm sorry.
- Gregory Brown: Oh, yeah. We need to look at the other . . .
- Josh Morse: Two other issues, really, to this. So, NCD and guidelines.
- Gregory Brown: Right. So, the . . . OK. So, other coverage decisions. Medicare does not have a national coverage decision. So, we cannot be in conflict with a retired coverage decision.
- Josh Morse: Correct. That one's OK.
- Gregory Brown: So, then clinical practice guidelines, which, as they were presented earlier, are variable. The conditions that we've chosen are consistent with some or most of those, again each of them kind of specify different tumors. So, it's hard to . . . it's not an apples to apples comparison would be my statement.
- Josh Morse: OK.
- Gregory Brown: Does anybody disagree with that statement? OK. OK. Does that complete it, sir?
- Josh Morse: It does. Thank you.

Gregory Brown: OK. Thank you for our speakers. Thank you for the agency directors. Thanks for our contract review. Thank you all for coming. Have a great weekend.