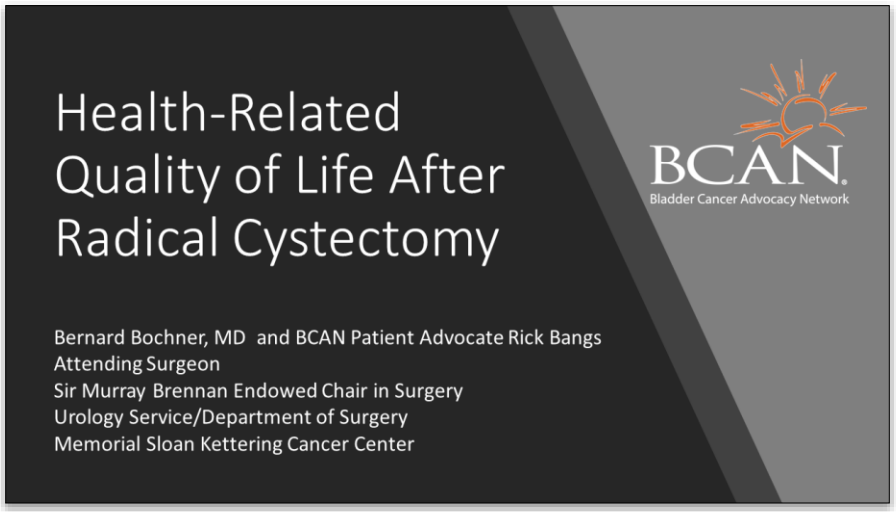


Dr. Bochner:

If I pause there for a minute, Rick, maybe I could bring you in and see if there's any questions or Stephanie, with respect to maybe how the study was designed and then we can get into maybe some of the outcome results.

Rick Bangs:

Yeah. So, you raised this incredibly important point about baseline. And so is it unusual to capture a baseline when people in cancer research do these kind of studies? Because I'm not aware that it is. And I think it's such an important point.

Dr. Bochner:

It certainly is logistically more challenging. What tends to happen, and it still provides some useful information, is that snapshot, right? So let's see how folks are doing three months after surgery and we can measure that in everybody. This type of study, it took a lot more effort because now you're longitudinally following folks. And you can see that even though 550 had agreed to join the study, there was a group that missed a fair number of the baseline measures. And so that was kind of anticipated. Not everybody, even though they have good intentions, they may not necessarily feel up to filling these out. And so that's why the numbers of folks begins to drop.

I think it's also important to recognize that not everybody follows the same course during their treatments, right? I mean, some people go right to surgery and other people may have spent several months receiving systemic chemotherapy before they went to surgery. During the follow-up period, everybody may follow a little bit different course as well, right? We hope everybody's cured and no additional treatments needed, but we know that some people may require additional care afterwards. And if their tumor comes back, that can also affect their quality of life as well. And in a subsequent study that we're working on, we're trying to figure out what those effects are as well. So there's a lot that's kind of happening as you march people through treatments, and it makes this kind of a longitudinal study a bit of a challenge to do.

Stephanie Chisolm:

I have a quick question too, Dr. Bochner. You did the study on the population at Memorial Sloan Kettering, and you do talk about the continent types of diversions, that includes the neo-bladder as Rick had, and also the Indiana Pouch type of a diversion. So do you see that you end up kind of 50/50 Memorial Sloan Kettering? Or is it really dependent again, on that age and stage and overall health of that individual?

Dr. Bochner:

Yeah. It's a great question. Who gets what? And why do people get that? So if we took a step back and we said, nationally, if we looked at the numbers, we know that probably on a national basis, only about 20% of patients get continent diversions. 80% of folks still are receiving ileal conduits. And unfortunately, that number has sort of been stubbornly stuck at 20% for quite a while, but it does vary from institution to institution and even within institutions it'll vary as well. So a lot of it has to do, I think with surgeons preference, their comfort level, their experience, their training. And so it varies. So in my practice, I can say that probably about 70%, 75% of patients receive a continent diversion, and about 20% to 25% to 30% maybe receive an ileal conduit. But that can vary. At our institutional level, it actually does turn out to be about a 50/50 split. But it does vary from institution to institution.

Stephanie Chisolm:

Right. Okay. This is great. And as far as having a lot of men participating in this survey, we know that the number is kind of equal to the incidents in the male versus the female population. But when you're going through and going to talk about all of these different changes that people saw over time, how can we tease out, because we know women do get bladder cancer, they're often diagnosed usually after some misdiagnosis or just a long trail of other treatments before they get to their diagnosis. How can we see this information conveyed to women as well as to men? Is this kind of thing that is representing really the overall population?

Dr. Bochner:

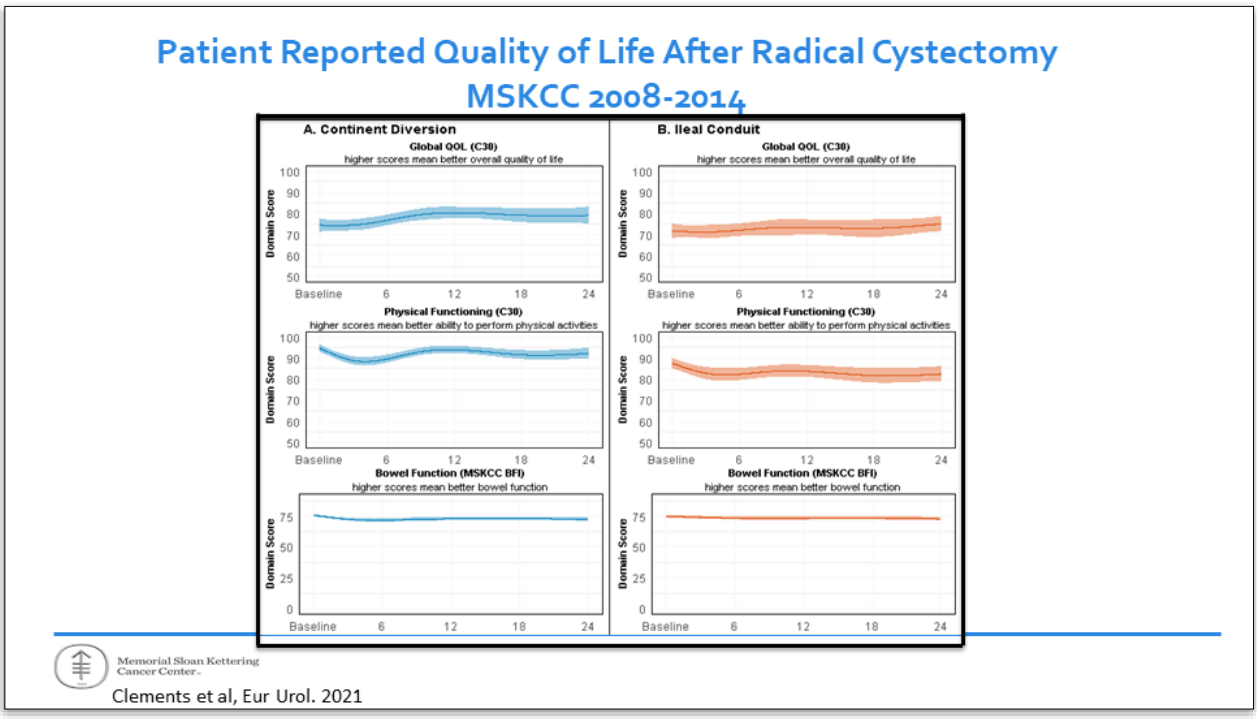
It's an excellent question. And so, because the numbers of women in many of the cystectomy series of patients that have been reported tend to be, it makes up the minority, it's maybe about, maybe 20% of the overall group of folks. And that kind of is where that number falls here in this series as well. What we're currently doing is we're taking a very detailed look at the subset of women that had undergone surgery as well. And one of the things that we included here was the female-specific sexual function measure for women and the male-specific sexual function measure for men. And so we have that information. And maybe even at a subsequent meeting, we can kind of go through the specifics for women because many of us really feel that we need to spend a lot more time and interest focusing exactly on sexual function and outcomes in women and that are undergoing radical cystectomy.

Dr. Bochner:

So what you see here, I think, and what I can tell you is that when we look at male and female, the global quality of life, a lot of physical functioning, bowel, the kind of other functional aspects, which we'll run through here is pretty consistent between men and women. The sexual function aspect is actually going to be... We're writing up a completely separate evaluation of that because we think it really deserves its own attention. So it's a very, very good point. But I think the takeaway for women who are listening to the webinar here, to the podcast is that these measures, I think for the other factors can pertain as well between men and women.

Stephanie Chisolm:

Great. Thank you. Well, we'll let you get back to sharing this information for a little bit.



Dr. Bochner:

Excellent. Okay. So these are probably the most important visuals I think that people can use. And what this basically shows is again, we've separated patients that have undergone the continent diversions in the blue and the people undergoing the ileal conduits. And again, we're not really trying to compare the apples to apples here. I want you to focus more on the trajectory, what happens over time? Okay? So if we look at sort of the top graphs here, these are measures basically of global quality of life. And what we would hope not to see would be that from baseline to those early measurements, a huge drop-off, right? Lower numbers here would represent major hits in global quality of life. And if it never recovered back up to that baseline, that would be what we would be most concerned about, right? That's telling us patients are taking a huge hit and they're not recovering.

Dr. Bochner:

And what these 400 plus patients told us is that simply not what they're experiencing. So if you look at the area here, these are their baseline measurements, and this is now the continent diversion group, looking at their global quality of life. And what you see is you don't see that major hit to quality of life. People are just simply not purporting that. And in fact, it continues to get a little bit better, or at least stays at the baseline as time goes on out to the 24 months. And this is basically the exact same thing that's seen in the ileal conduit population. So here's their baseline global quality life measures. Keeping in mind that higher scores mean better overall quality life. And you don't see that major drop. People are not reporting that. And they're able to maintain their baseline quality of life throughout the study.

If we look at measures of physical functioning, okay? So higher scores here mean better ability to perform physical activities. This is exactly what you would expect, right? So after major surgery, people's ability to perform their physical activities does take a drop, right? And I'm sure Rick could speak directly

to that. But after they get beyond that first three to six months, what we see in the continent diversion group is that they get back to their baseline level of physical activity. We see this same drop in the patients undergoing ileal conduits. It's a drop, but it's not a massive drop in their physical activity, but it's definitely a drop. And then over time, it gradually begins to make its way back to baseline. Again, same thing that occurs in bowel function, okay?

Now, why would bowel function be interrupted? Well, it's an intra-abdominal surgery when the bladder is removed and the reconstruction is done. The urinary reconstruction uses a segment of the intestinal system, whether it's an ileal conduit or a neo-bladder or some sort of continent reservoir that's catheterized. And so what we see here is that there is a slight drop in bowel function reported in the early parts of the recovery. And again, I think that most people who've undergone surgery would say, "Yep, my bowels were a little out of sorts there for the first couple few months," but then they get back to what they report as sort of their baseline level of function. In the ileal conduit patients, you can almost not even discern much of a change in bowel function over time, and it stays stable as we move on.

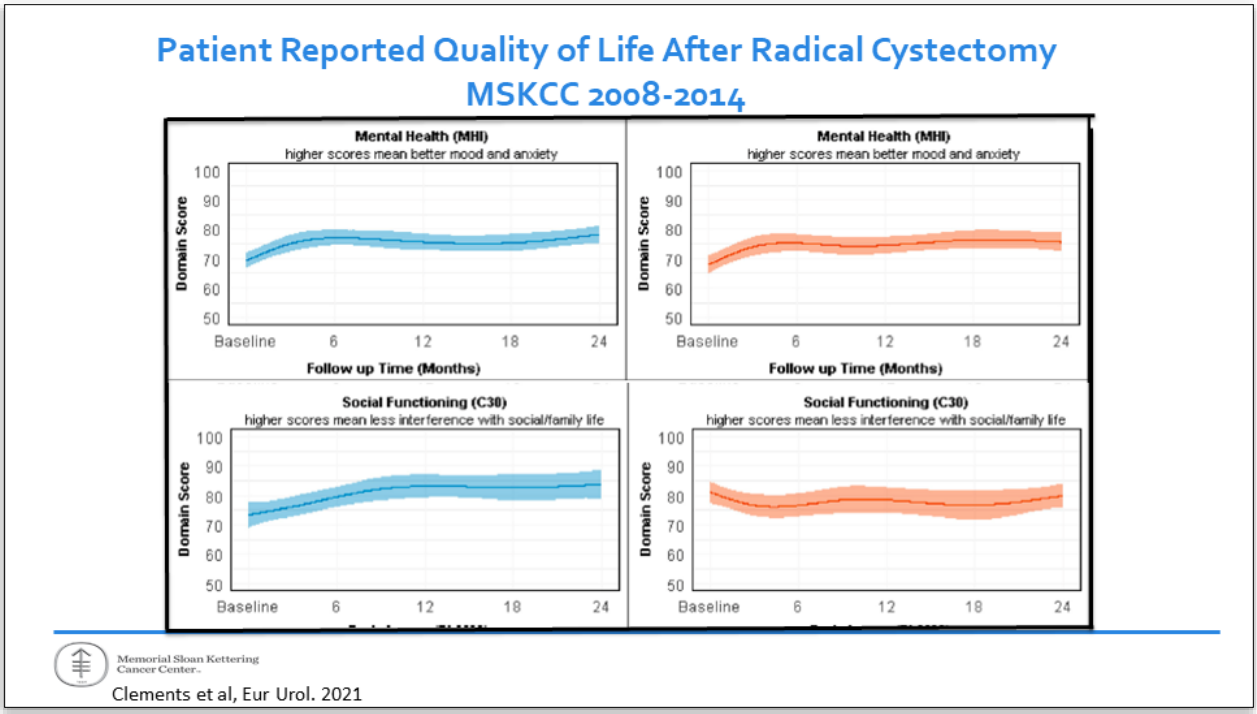
Stephanie Chisolm:

Yeah. I just asked a question about that because the neobladder, for reconstruction that way, uses a larger portion of the intestines. Do you think that has something to do with why there's more of a dip there in bowel function than there is in the folks with the ileal conduit?

Dr. Bochner:

Yeah. It absolutely may be. And again, I think that if you... You can see and numerically we can identify there is a little bit of a drop-off here, but what's very satisfying to Stephanie is that we don't see a major drop-off, right? Where we see this pressed down to these levels, which would really be significant bother due to their bowel function. So no question things change. I think that it's absolutely reasonable to assume that because a little bit larger segment is used for these internal reconstructions, that they may take a little bit more time to settle down. But I think it's important for folks to recognize from these three panels, what this told me is, number one, there's going to be a recovery, there's going to be some time, you're physically going to need to recover from the surgery, but you are not going to be devastated by this operation, that your quality of life is going to remain high.

And that once you get through the early part of that recovery, there's every expectation that you're



going to be able to get back to the physical activity that you were doing at baseline, your global quality of life is going to get back to baseline, and that your bowels are going to take a little while, maybe to settle, but that's not going to be what drives a lot of the problems following surgery, which was, again, I think really important information for us to see. Honestly, this is what I've been seeing for a couple of decades now doing this, but it was very gratifying for patients now to be able to see this. And now I can tell you, this is what patients report. So these are very reasonable expectations. Well, what about some of the other nonphysical aspects? What about mental health, for instance?

Dr. Bochner:

And so here now, again, higher scores mean better mood, improved anxieties, improved levels of an anxiety, and you can see that, here's baseline, obviously people are stressed moving into surgery and a little bit of the unknown, and you can see that rather quickly, mental health scores are reported as better, and they stay stable if not improve a little bit for both the conduit or the continent diversion, as well as the conduit patients as time goes on, okay? Social functioning. I think this is another really important aspect that many people have moving into surgery. Am I going to be able to get back to work and interact with my colleagues? Am I going to be able to have good interactions with my family and my children, grandchildren? And that's exactly what we see here. So higher scores again, mean less interference with social and family life. And following this lower baseline measurement in the continent diversion folks, you could see this steady, nice increase and it actually returns to a level above their baseline.

Now, interestingly in the ileal conduit patients, we saw that social functioning actually was a little bit better at baseline. There was maybe a little bit less interference at baseline, the reports, with their social and family interactions, but that did change a bit. So they did see a drop in the early periods, but by about six months, that began to return back to their baseline levels, okay? So a little bit different again, and this may represent just the differences in the age of the patient, the overall health of the patient. It may be that it is a little bit tougher for people who are average age 72 compared to average age 62 early on undergoing this type of a surgery.

Stephanie Chisolm:

When I ask, did you tease out or have any opportunity to interview to really understand, for instance, maybe that change in social function for patients with an ileal conduit, until their comfortable and confident in how to manage that appliance might have something to do with anxiety about having a leak or we talk about this, we hear from patients all the time that they're worried about having a leak or what if somebody knows that they have a bag and that limits their outside activity. Have you done any deep dive into some of that with maybe follow-up interviews with participants?

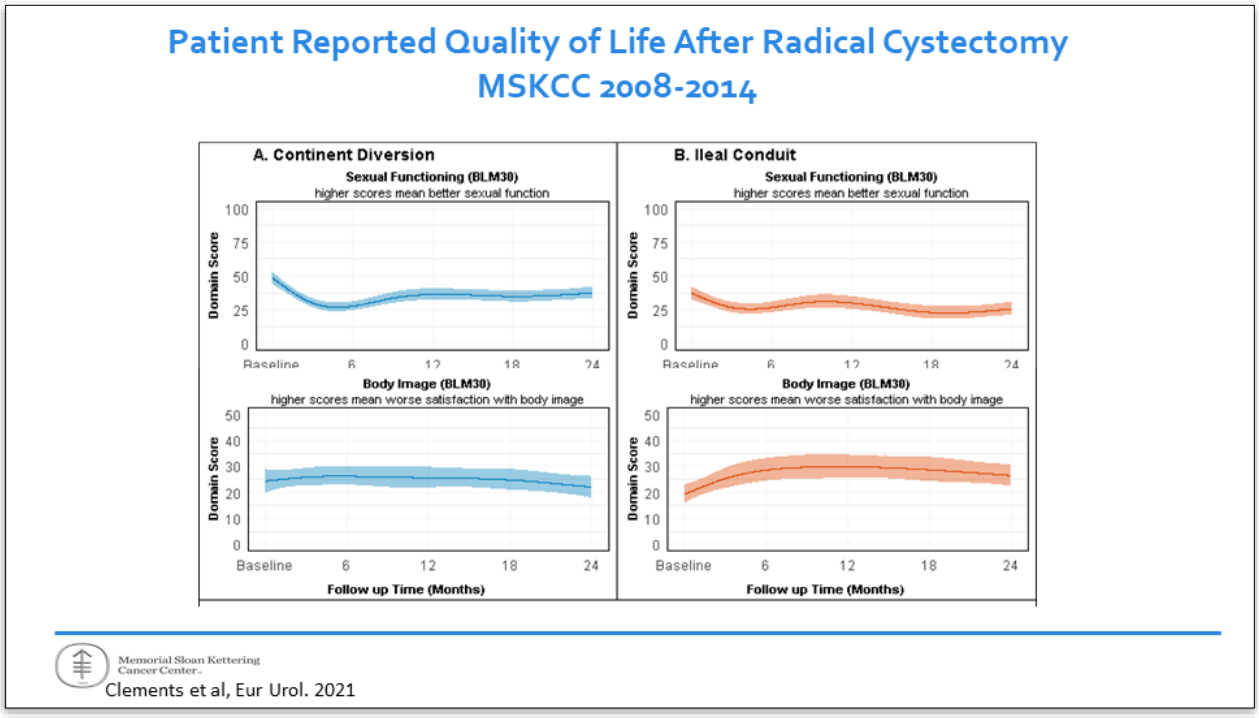
Dr. Bochner:

So the other aspect of this study, not represented by this data, was a separate, what we call idiographic evaluation, which is an interview technique. So these standardized forms basically are exactly that. They're forms. They're predetermined questions with various scales that people can answer. So Stephanie's making a very important point, which is you get a lot of information, but you're only getting what you're asking and you are limited because it's a set question and answer. And we recognize that. And one of the early collaborators in this study had a particular interest in this interview technique, in which open-ended questions are asked to folks, and then their responses are recorded and then coded. And so we have an equal mountain of data, of interview data that actually is undergoing analysis right

now. And we have begun to start getting some information out through that. And I can tell you that a lot of that information is additive to what we get from the standardized forms.

Dr. Bochner:

And so it's incredibly important to recognize that while many of these forms are validated, and this is what's available, there's so much more that patients want to tell us. And it will vary from person to person. And so super important. But to specifically answer your question, why maybe are we seeing the social functioning drop, it could be related to this. And so these were the two domains, the two areas that we looked at that did not return to baseline, okay? And I want to focus on the bottom one first. The bottom ones focus on body image. So here, higher scores mean worse satisfaction with body image. So



here, you don't want to see the lines going up. And as Stephanie had alluded to, so here are the neo-bladder patients, continent diversion patients, where body image essentially is unchanged, maybe slightly improved by the end of the study. And that's not what we found with the ileal conduit patients.

Dr. Bochner:

And this has been identified in other quality life studies done in patients undergoing bladder cancer, which is one of the things that is not necessarily going to favorably change in patients with external bags is body image. And here we do see increased scores, which correlate with worse satisfaction in body image. And you're right. This may translate as well to concerns about how comfortable they are with their appearance, with the ability to control the bag itself, the urine from leaks, other things until they get settled. Interestingly, even after two years though, of using the appliance, the body image domains really never returned to normal in the ileal conduit patients. So this was one area where I think we need to try and make some improvements for folks.

The other area that also showed a change over time was sexual function, okay? So here now, higher scores mean better sexual function, lower scores mean worse. And you can see that whether it's for the continent diversion patients or the ileal conduit patients, there is a drop-off in function, which basically

is sustained over time, okay? Now, why is that? Well, it is interesting here. If you look at the baseline measurements of sexual function, what I could tell you is that these are probably not unusual levels of measurement for men who are at this age group. We know that overall men's sexual function can decrease as we age.

We know that again, because there's a 10-year difference between the continent diversion patients, younger, 10 years older in the ileal conduits, that their level of function is even more depressed, which again, 72 medium age versus 62. The other important aspect here is that unlike prostate cancer surgery, where we're much more able to do nerve preservation because of cancer-related factors, safer to spare the nerves and many men undergoing prostate cancer surgery, and they're also in general, younger, we can see a higher degree of maintaining sexual activity. For invasive bladder cancer, high-risk bladder cancer, nerve-sparing surgery, for many folks, we just simply can't do because of cancer-related factors, where the nerve bundles are located in relationship to where the tumors are. And even if we do nerve-sparing surgery in many men where their function has already been depressed, it may not work quite as well.

Dr. Bochner:

So I think we can certainly physiologically understand this, but we're taking very hard looks at each one of these groups individually, because again, this is just sort of the overall groups that you're seeing. And within each one of these groups, we're going to have very different populations of patients. You're going to have some men coming into surgery with very good sexual function with a partner and an interest to maintain that. And those are the folks I think that we need to spend a little bit more time thinking, can we do safe nerve preservation surgery? And if not, can we provide alternatives, other erectile rehab options? Because that may drive a lot of their overall quality of life.

Dr. Bochner:

On the other hand, and maybe some older men who have already lost a fair amount of function, maybe they're widowed, maybe they don't have a spouse or a partner, where sexual activity is not what's driving their overall quality of life, they may be more interested in getting back to being with their social group, maybe being able to get out and go golfing or play cards, or maybe go swimming with their group of friends. And so these are the things that we need to focus on to be able to kind of help them get better. But I think that these numbers are real, and these are things that we have to be able to show folks, "These are the things that you may experience after surgery."

Rick Bangs:

So can I ask a question? So you've got this great data across time. In the interviews, did you get any sense, particularly from baseline to three month period, some of the fluctuations that happen between the points, because I mean, clearly you're going to struggle with continents and leaks in that first three months. So you're going to struggle more, I am suspecting with sexual function, the bowel issues that you mentioned earlier. So did the interviews tease out any of the kind of fluctuation between the baseline point and let's say three months?

Dr. Bochner:

Well, so three month is really the first evaluation that we did here, right? And Rick, again, I think you have this unique perspective having gone through this, you know that there's a lot going on in that first three months.

Rick Bangs:

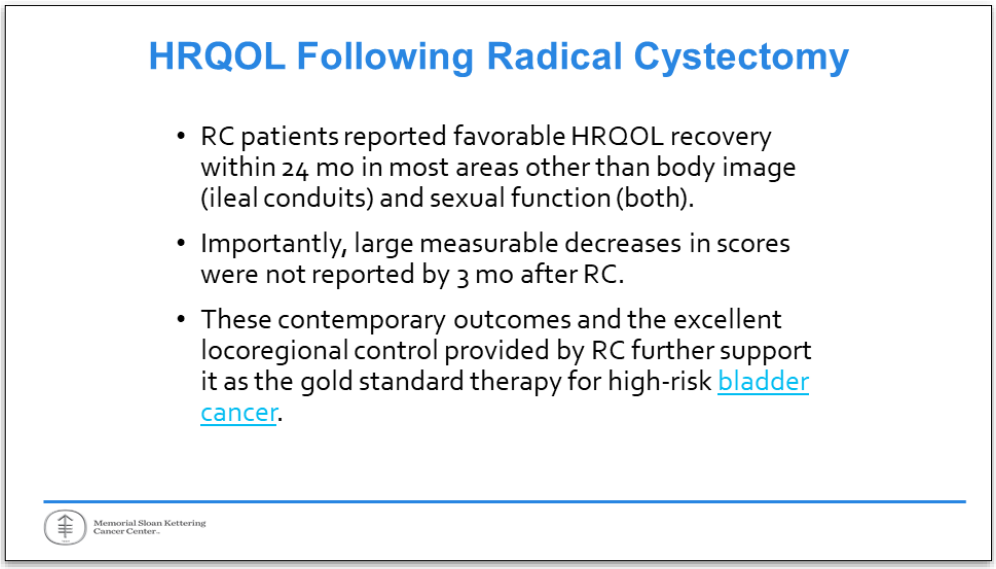
Yeah, exactly.

Dr. Bochner:

Right? I mean, the first month you're trying to figure out up from down, trying to get your bowel settled and you're bouncing between constipation and loose stool and at the same time, your urinary sphincter is working on getting its tone back and your neo-bladder is ensuring its capacity. So you've got a pad that's leaking, you're trying to find the bathroom and you're just exhausted, right? And so that sort of sums up the first four weeks easily, of the recovery. And we recognize that there is that early recovery period where I think people are just taking that major hit from surgery.

So what this study was really trying to focus a bit on, and we lost some of that early change that you're referring to, is where we were asking, okay, so what's next? Right? So once people really feel like, okay, you know what? I'm eating, I'm actually doing a full-day's activities now, I can see the light, I'm getting more control now, maybe I'm down to a safety pad in case I cough or sneeze, or if you have a conduit, I've got this figured out. I haven't had a leak in a good couple of months and I'm able to find a comfortable position to sleep on and I've got clothes now, I'm not so worried that everybody's going to stop me and go, "Oh, you wearing something under your clothes there?"

And so that's kind of when we wanted to sort of begin to start seeing what happened once people sort of made it through that initial tunnel. And we know that it's a good three months, at least for many folks that are going through this. And so that's when we started our measurements and we wanted to see. And we figured by a year, year and a half, a lot of folks have sort of settled in as far as their continents goes, if you had a neo-bladder, your nighttime control probably is continuing to get a little bit better even beyond that. And for the ileal conduit patients, for the most part, they've kind of figured out life with the appliance. For men, at that point, by year, year and a half, most of them have freed their wives from having to do all the changes for them. And they've learned how to take ownership of the bag and they're doing the changes.



Dr. Bochner:

And so that's what we really wanted to see. And again, it was quite gratifying to see that many of the really important domains are not taking that huge hit. People are really getting back to the things that

they love with the caveat yet that this is not a perfect surgery, that there are some of these measurements, such as what we're seeing here that are going to change and are going to take some adjustments. And fortunately, there are options from a sexual function standpoint and they're different obviously between men and women, and there's some adjustments that are going to have to happen, especially in body image if you have a conduit.