



Question and Answer

Stephanie C.: Thank you both so very much. I think you've covered some of our initial questions. It was comparing cystectomy rates to tri-modality therapy rates, and I think you've covered that very well. There was a question that kind of came up that was looking at BCG and non-muscle invasive disease and whether tri-modality would be in lieu of perhaps a BCG treatment or any other options for non-muscle invasive disease. Would you guys talk a little bit about that? Is it being done at all and that non muscle invasive space?

James McKiernan: I'll take a shot at that. So, in general, non-muscle invasive bladder cancer is not treated with systemic chemotherapy and relatively infrequently is treated with radiation. And so in lieu of BCG for things like high grade TA, T1 or carcinoma in situ, we don't usually substitute systemic chemo or radiation. Jason maybe can talk about that, there have been a few trials about using it specifically in people with high grade T1 bladder cancer, which is failed BCG, and I don't know if you want to comment on those, Jason.

Jason Efstathiou: Great. As Jim says, it is not standard to use chemo radiation in non-muscle invasive bladder cancer. There is a study that finished accruing or taking in patients last year that looked at setting of recurrent BCG refractory, high grade T1 bladder cancer. So the patients who had T1 bladder cancer where the

cancer was recurrent, and they had tried BCG but it didn't work, and there was an attempt at using chemo radiation tri-modality therapy in that setting. But I have to emphasize that was in a trial setting and those results are not yet available. But I certainly think that it is a reasonable option to consider for patients who may have recurrences of non-muscle invasive disease that have exhausted intravesical options, like BCG, and are not cystectomy candidates. And that select situation I think it is okay to at least have a discussion whether or not tri-modality therapy makes sense.

Stephanie C.: Thank you very much. Dr. Efstathiou, this question is for you. What are your thoughts on Proton Therapy versus IMRT radiation? Are they both equally as effective? Proton Therapy only having better targeting advantages. Is there any difference in this?

Jason Efstathiou: There really isn't any experience using proton therapy for bladder cancer and to be honest, I can't see a particular benefit to proton therapy in the treatment of this disease. The one problem with the bladder is it's a highly distensible, organ, meaning its size fluctuates depending on bladder filling of course, and that sort of uncertainty of bladder filling would make Proton Therapy challenging in a number of circumstances.

Stephanie C.: Thank you. You mentioned a number of different survival rates. There's a question that came in, did the survival rates take into account age and normal rates of death? I think people were looking at those ways that you had listed early on in your slides.

Jason Efstathiou: Yeah, those rates are, what was called "an average for patients" that were in those studies. That being said, there is a range of ages and other issues in those studies. And so we believe that those numbers represent an average, but certainly they would need to be tailored to any individual patient, depending on circumstances, whether it's age, comorbidities, other health issues and particular details about the bladder cancer. Very importantly, the stage affects things and other factors.

Stephanie C.: Thank you. If there needed to be a salvage cystectomy is the neobladder an option and if not, why is that?

Jason Efstathiou: As I mentioned and maybe Jim can talk to this as well. There isn't really an experience of doing neobladders, there's a concern that using the bowel to recreate the bladder, when the bowel has had exposure to radiation may be particularly challenging. But I would defer to the surgeon, Dr. McKiernan, to address that.

James McKiernan: Our experience is it can be done it shouldn't be approached as something that can't be done. The risks and the outcomes are not quite as good as they are in the primary setting because of what Dr. Efstathiou said but also because the continence, the control mechanism at the base of the bladder is not quite as capable of adjusting and healing to the neobladder. So it's feasible but urinary leakage or incontinence rates tend to be a little bit higher and the rate of neobladder creation at the time of salvage cystectomy is fairly low. So there aren't that many surgeons and or patients who feel comfortable doing it. But it has been done, it can be done, and it's not absolutely contraindicated but the outcomes are not quite as good.

Stephanie C.: I just wanted to mention that not everybody is a candidate for neobladder, even though they would prefer that, and there are other webinars online that address the different types of diversion, but could you just mention that briefly as well Dr. McKiernan?

James McKiernan: For sure. That's true with or without radiation. So, it's the expectation that most patients coming into this kind of decision-making process, that it would always be better to have a neobladder whenever possible, but other factors such as age and other medical risks and even the stage and state of the cancer may or may not preclude creation of a neobladder prior abdominal surgery, prior intestinal conditions. So not everyone is a candidate for neobladder even if there is no radiation in their background or history. That's definitely true. And customizing and selecting the right kind of urinary diversion for each individual patient is really critical to having a quality of life after cystectomy making sure the patient is involved in that decision.

Stephanie C.: Dr. McKiernan can you mention why a patient with a squamous differentiation might not be eligible for tri-modality therapy? Is there some particular reason why?

James McKiernan: Well, the pure squamous histology is a slightly different form of bladder cancer. What's more common though, and I think it's sometimes misunderstood, is that many urothelial cancers will have a component of squamous differentiation, that's far more common than pure squamous cell carcinoma. And in those situations, as was mentioned in Jason's review that those patients do tend to be candidates. So urothelial carcinoma with either adeno or squamous features can be treated with chemo and radiation, or with surgery and proceeded by chemotherapy. In fact those patients in general are at higher risk of recurrence no matter how they're treated. So, the combined multi-modality therapy is usually more indicating in those situations, but the pure squamous cell carcinoma tends to be slightly different. Not that they're not radio responsive or radio sensitive, but those are fairly rare in the United States probably about

1% of all people diagnosed with invasive bladder cancer, have a pure squamous cell carcinoma.

Stephanie C.: Great thank you so much. Would co-occurring lymphoma that is not part of the stage two bladder cancer be exclusionary criteria or make a patient not eligible for tri-modality therapy?

Jason Efstathiou: Obviously in the case of two different cancers they need to be treated individually but in and of itself having another cancer diagnosis does not preclude doing tri-modality therapy. You just have to take care if there are therapies being given at the same time for two different cancers that they don't sort of interact in a bad way. But in and of itself, another cancer diagnosis does not preclude tri-modality therapy for bladder cancer.

Stephanie C.: Great, thank you. Dr. McKiernan, maybe can you mention something, say a little bit more about the implications of carcinoma in situ.

James McKiernan: Sure. Carcinoma in situ is a unique component of bladder cancer, it's really a cellular process. It's not a tumor per se. And when you see it in the bladder, it tends to be relatively diffused, sometimes even difficult to diagnose or find and is difficult to control with focal therapy, whether it be surgery or radiation. Because it's difficult to even identify where it's located. So no matter what treatment you choose, if it involves keeping the bladder, any presence of carcinoma in situ will increase the probability of having cancer again. We sometimes think of it as a field or global defect of the lining of the bladder that prompts new tumor formation in the future. And most people with carcinoma in situ even when you look at the genetic level, have some different alterations than patients who have a tumor, papillary tumor or physical tumor. It's one of the reasons why a non-muscle invasive disease we perform surgery followed by BCG, which tends to coat the entire lining of the bladder and cause a diffused immune response to try to combat carcinoma in situ. So you'll oftentimes hear a doctor say things like, "Well we were going to do this, but you have carcinoma in situ so we're going to do that. Whether this or that be BCG or not BCG surgery radiation cystectomy. It's definitely a factor in the natural progression of bladder cancer.

Stephanie C.: Okay, thank you. There's another good question in here. And that would be, why aren't more urologists pushing tri-modality therapy?

James McKiernan: I'll take that one first. And then they hand it over to Jason. I think it's a complex question. I think partially it's an awareness issue. And the results that we saw tonight, maybe not everybody is aware of how well it works. It also may be that in their local environment, they don't have experts who are quite as good as the

team at Mass Gen at delivering and coordinating this kind of care because it does require multiple team members in place. You saw the data from Toronto where there's a fabulous multidisciplinary team. But that doesn't exist necessarily in every practice or every community, and then it may very well be that they're convinced that surgery is the only option because the person counseling the patient is a surgeon. So, there's just like in any area of medicine, there's some inherent biases in people's opinion and the absence of a real level one randomized trial, sometimes biases become the driver of recommendations. We saw the same phenomenon when neoadjuvant chemotherapy was first proven in a randomized trial to improve survival with cystectomy, yet it took over a decade for even 40% of patients to receive that prior to cystectomy. I think in America right now, maybe we're up to 45 or 50% of people having their bladder removed, will get new adjuvant chemotherapy first so. That was proven in actually multiple trials to improve survival. But it's taken a long time to kind of change practice.

Jason Efstathiou: Yeah, I think Jim's comments are spot on. I think and you can't just blame the urologist because many radiation oncologists are not comfortable or familiar with bladder sparing therapy because they've never been exposed to it. They've never seen these patients and had opportunities to treat them. And so they sometimes are also part of a roadblock in terms of promoting this as an option. I think that ultimately the truth of the matter is that something that I said earlier that seeing these patients with all specialists is the best model to allow for open discussion of options. The other important point is the awareness point that Jim mentioned. If patients are aware that this is an option and they go and ask their urologist that they want an opinion about, tri-modality therapy, I think that over time is going to lead to a much greater growth in this as an option. So patients being empowered to ask about options to be aware about options, and I think this is where BCAN becomes such an important, sort of central piece of the advocacy is by opening up and providing information to patients, letting them know that there might be options in certain circumstances that they should ask about. That will help sway urologists to say, "Hey, I at least have to discuss this with a patient and I may have to refer them to other specialists to hear about this." And then as those urologists see successes over time, they'll grow more and more confident. As radiation oncologists around the country do this more and more often, they'll grow more confident. And as Jim says, it may take a decade or more, but I think we're at that tipping point where this is starting to happen and I think we're going to see real growth over the next decade in this treatment paradigm.

Stephanie C.: Great. Thank you both so much. I have one more question and then we're going to conclude the program. For those with a single kidney due to your urothelial

carcinoma in the renal pelvis and they're now having a recurrence is tri-modality therapy an option?

Jason Efstathiou: Can we can both answer this. I mean, I think it sounds like it's a solitary kidney. No, I think the issue is what chemotherapy to choose. What is the renal function? As I highlighted, there are different chemotherapeutic options and so I think tri-modality therapy remains an option in this scenario. I think just that the treatment needs to be tailored to the renal function, in particular, the choice of chemotherapy.

James McKiernan: I would agree. I concur completely. If it's a recurrence in the bladder, its muscle invasive. Key is just to preserve that function of the contralateral kidney. So whether it be the location of the tumor in the bladder, the function of the kidney, the chemotherapy chosen, you really wouldn't want to do anything to compromise the solitary kidneys function.

Stephanie C.: Thank you guys so much. This has been a wonderful, wonderful program. I would like to once again thank Bristol-Myers Squibb, EMD Serono, Pfizer, Ferring, Genentech, Photocure and Merck for making this webinar series possible.

