**Question and Answer**

**Stephanie C.**: "Are preservation strategies appropriate for T2 tumors with variant histology such as micropapillary?"

**James McKiernan**: All the variant histologies particularly micropapillary tend to be less likely to respond to chemotherapy both locally and systemically, so that's a very specific high-risk subsets of patients. In general, we're very cautious about recommending anything conservative to those patients. It is possible to have a pathologic complete response with muscle invasive variant histology. Some patients who have their bladder removed will find no cancer even if they have micropapillary, squamous, adenocarcinoma, glandular features, but it's less likely than if they have pure urothelial cancer. I would say caution is advisable there.

**Cheryl Lee**: I agree with that. The other reality is that those patients that have alternate histologies are generally not at the center of the patient population undergoing this trial. A lot of times, those patients may even be excluded from some of our research, some of the larger clinical trials, so we don't fully understand what the natural history of some of those tumors are, so I also think we must move with caution in patients who have those variant histologies.

**Stephanie C.**: Of the 14.7% of tri-modality therapies who have patients who have recurred and go on to a radical cystectomy, what are their general oncologic outcomes? Is radical cystectomy successful for them as it would have been if it had been used as a primary treatment?

**Cheryl Lee**: We have to remember again over time the number of patients who have to have their bladder is shrinking after the tri-modality therapy in part because we're getting better at selecting patients frankly, but there's still a small percentage of upwards of 10% of people that may not survive their cancer long term even though they did have to have a subsequent bladder removal, so sometimes, the window of cure has closed, so we have to keep that in mind. The majority of patients who are having tri-modality therapy can be salvaged with radical cystectomy or still achieve a cure if they're caught...
early, but certainly there is a proportion of patients and that used to be probably closer to a third I would say. Now, it's closer to 10% or 15%.

**James McKiernan:** Yeah, I would just add there that we must be cautious because when we only operate on people for whom a treatment didn't work, it is inherent that those patients are higher risk group than everybody else. If someone receives platinum and radiation and their cancer relapses, their outcome with surgery is going to be worse, not because they chose that treatment but because it didn't work. When patients respond to a treatment that is an indicator that their cancer is less aggressive or more sensitive to chemotherapy, but if you only analyze surgical outcomes on chemotherapy refractory patients, it will appear that the surgery does not work very well.

**Stephanie C.:** Can either one of you comment about using narrowband imaging during cystoscopy or in the case of blue light, using the [inaudible 00:54:23] blue light, does it help to better see and determine if there are cancer cells or pre-tumor conditions? It seems this would improve predictions and decisions about whether to have a cystectomy.

**Cheryl Lee:** The blue light technology I would say has certainly increased our ability to detect cancers beyond our standard white light type of cystoscopy. The patient context that we're talking about for the blue light is the patient with earlier stage cancer, not the group we've been talking about mostly this evening. I just want to make sure that's clear. Certainly, the blue light can help us increase not only our detection of tumors on the surface, but some tumors that are invading into the layer below the surface and some of the surface cancers that are high risk, the carcinoma in situ that we believe are precursors to those that will invade. It has a role of improving our detection of cancers. It's not widely available across the entire country, although certainly many academic centers have access to it and some large urology group practices, but access can be an issue. Our guidelines that we use to guide treatment for patients with earlier stage bladder cancer does advocate for the use of the blue light when it's accessible to help improve our detection of cancers and frankly our studies that have been done have shown that using that technique can help improve our actual clearing of cancers from the bladder so that the rate of recurrence is less over time for those patients.

**Stephanie C.:** As far as white light in terms of it showing that are imagery of the blood vessels, does that make a difference either if somebody is using a white light cystoscopy? I'm sorry, narrowband. I'm sorry I got that confused. Narrowband imaging?

**James McKiernan:** Yeah, sure. Well, narrowband imaging does increase detection of tumors. It's not quite as sensitive as the blue light fluorescent cystoscopy, so it doesn't have quite the same amount of data to support it in the setting of non-muscle invasive bladder cancer, but it is something that is available and will increase detection. I think the question there was a great one because these technologies are not generally talked about when we speak about muscle invasive bladder cancer because they're oftentimes not as relevant in cases of muscle invasive bladder cancer, but when you're evaluating a patient post chemotherapy who appears to have no cancer and you're thinking about doing something other than a cystectomy, I'd actually do think they make a difference to look for that carcinoma in situ, that hidden subtle early high-grade recurrence that might actually tip you over to say, "You do need a cystectomy."

In general, we do try to use blue light on post-chemo evaluations because we even want to know if they have residual non-muscle invasive disease because we don't want to watch them if they do.
Cheryl Lee: I should also comment that some years ago when I was still at University of Michigan, we did several studies trying to really determine the ability to use a nonstandard type of chemotherapy for bladder preservation, so it wasn't the typical therapies that were used. At that time, it was gemcitabine. Now, that's been shown to have reasonable results and be similar to some of the more standard therapies and bladder preservation, but at that time, it wasn't standard. What we found though is that even at three to five years more than two-thirds of the patients who we had carefully selected and had undergone tri-modality therapy, when they recurred, it had tumors that were just on the surface.

Cheryl Lee: We managed many of those patients just with intravesical therapies and we were able to salvage the vast majority of them and still to preserve the bladder. There's certainly a role for the patient who is very committed to bladder preservation. There is a role for intravesical therapies after systemic chemotherapy and/or radiation in the bladder, but sometimes these tumors can be managed conservatively and those are of course non-invading cancers, superficial types of cancer.

Stephanie C.: I'm going to ask one last question and then we'll conclude tonight's program, but if you had a crystal ball, absolutely you would be able to answer this one a little more clearly, but what is the recurrence rate after 10 years for cancer-free survival with bladders that have been preserved as compared to perhaps bladders that have been removed? Is there a way to do a comparison at that 10-year mark?

Cheryl Lee: Well, this is a tricky thing because a lot of the data that we have for bladder removal after surgery, the patient population is a bit different than the patient populations that we have who have undergone tri-modality therapy and particularly more recently the group undergoing tri-modality therapy has gotten to be highly selected. I will say that a study was published within the last two years. I think it was 2017 perhaps out of Canada and they actually tried to compare, looking backwards, so it's not perfect by any means, but looking backwards, they compared something like 55 or 56 patients who had undergone tri-modality therapy to those who had undergone bladder removal.

Cheryl Lee: Although they don't have 10-year data in the shorter term and this is the shorter term, probably under two years, the outcomes were similar, and these are patients that were not so heavily selected. A third of these patients had carcinoma in situ. Probably about 15% in each group had swollen ureters. They tried to use a statistical method called propensity analysis to match the patient as if we were trying to randomize them but certainly it's not the same. That is a study that I can point to that's somewhat recent, so it reflects kind of what we're doing more recently and try to compare the tri-modality therapy group to the systemic group.

Cheryl Lee: It's a very difficult study to even think about trying to do if we did it the old-fashion way of getting a group of patients and randomizing them because patients often have very real ideas about what kinds of therapy they do or do not want to have.

Stephanie C.: Well, thank you very. I think this has been a phenomenal program. I'd like to once again thank Bristol-Myers Squibb, EMD Serrono, Pfizer, Ferring, Genentech, Photocure and Merck for the making the Patient Insight Webinar series possible. Thank you so much, Dr. Lee and Dr. McKiernan for a phenomenal program.