I'd like to mirror Matt's word in thanking BCAN for organizing this webinar. I think it raises some very important points that pathologists need to be aware of especially as we think about the future and how we are able to best present information to patient. Thank you also to all the patients who are willing to join us today and also provide feedback for us. I think, you know, it's very important to have an ongoing dialogue with everyone engaged to make the best progress in this disease.

To run through a brief outline of what we will be going through today, we will start off with a discussion of the role of the pathology and pathologists. We will run through some basics as tissue sampling and diagnosis. We'll go through a few sample patient pathology reports and some of these may look familiar to some of you. Clearly, we don't have time to go through every possible disease state but we can
We'll talk about some of the diagnostic fields that as a patient, you may see as you review your report and how you interpret them. We'll wrap up with a brief discussion on I guess, a bit of the good, the bad, the ugly of second opinions; why they’re useful and what to be careful of. To start off, let’s just review pathologists and pathology reports. I feel that nowadays versus 10 years ago, the first point is something that I don't frequently have to say as much. I think patients are beginning to be more aware of pathology and pathologists.

Just to be sure, everyone knows pathologists are physicians. We go to medical school and part of our sub-specialty training after medical school is in pathology and we specialize in tissue or laboratory diagnostics. For example molecular testing, blood tests if you get your CBC or white count, urine cytology, et cetera. These are all parts if pathology practice. We use at least on the tissue-base side and cytology-base side a microscope to diagnose disease on biopsy or surgery specimens. We also perform special testing. This includes genetic testing as it’s indicated. We're going to see more and more of this emerging over time in the field of pathology and in cancer specifically.

We also write the pathology reports to summarize the findings and we'll be going through this in a bit more detail later on the talk. Finally, we made sure that the reports get integrated with patient care. Typically, these reports get discussed with the treating physician and in bladder cancer, this is the oncologist, the urologist to make sure that everything’s put together and it makes sense clinically. There are those of us who also discuss these reports to the patient if the patient’s requested it.

To run through some of the basic terms you may hear when it comes to pathology, I'll talk about the flow of tissue and in this case, urine specimens as well. Typically, what we see here is a flow of how, in this case, tissue is processed. It starts off with a patient visit to the urologist’s office or clinic or in some cases, the operating room if there’s going to be a cystectomy, or a nephrectomy, or ureterectomy, et cetera. Usually, when tissue is sampled - this could be a biopsy, it could be a urine sample, it could be surgery material.

We move from the urology or the OR stage to the pathology department where the specimen is received, it’s sectioned. We make sure it belonged to the correct patient, that the clinical information is present. From that point, it moves to what we call Grossing. When you look at your report, you may see a section that says Gross Description. Essentially, you’re in this part of the process here where the specimen is described.

We say, "A specimen is received, labeled with this patient's name, with his medical record number, is
designated as a bladder biopsy. It consists of three pieces of tissue measure this by this, by this centimeter. The specimen is cut and is placed in sets and fully embedded." That description takes place about midway in the process.

The tissue moves into a laboratory where it undergoes a series of chemical changes. It gets put into a racks block and it gets cut, so we end up making slides. These slides then go to residents and pathologists to be reviewed. As part of this, there could be additional testing such as immunohistochemistry or molecular diagnostic. This gets put together into a comprehensive picture as a pathology report. This pathology report then gets transmitted to the medical record and the urologist, in this case. If needed, there is a further discussion of the case.

To go through it in a bit more granular detail what's entailed, so the gross analysis or examination that I mentioned. Typically, the material will come to us, biopsies, transurethral resections will come in this sort of container labeled with all the information. Surgery specimens are much larger and will come in a larger container. Essentially, what we will do is evaluate the tissue by eye. We document and describe what tissue is present. We make sure that it matches with the operative notes to make sure nothing's been missed or accidentally discarded.

If it's a larger specimen like a cystectomy, it gets dissected into smaller pieces. These smaller pieces some of, which includes the margins, some of it that includes the staging status, some of it that make sure we sample representative areas of the tumor. Then, it's placed into tissue cassettes and these cassettes go into formalin to preserve the tissue architect and then, they get further processed to make glass slides that we use for pathology evaluations.

In this photograph here on the bottom, this is a cystectomy specimen from a patient. It’s been opened along the anterior aspect and in this case, you could see the tumor that's present and here is the inside of the bladder. You could tell in this case, the tumor is filling a large part of the bladder. The part of our job in this case is to sample the different margins, so the ureters, the urethra, and so we take sections of those. We further open up the specimen. We look at the margin status. We cut through the tumor.

We describe how big it is. We describe how deeply we think it invades. We section a large amount of this tumor and put it through and then, we'll sample some background bladder for example. It’s a pretty involved process with some guidelines around it and how we approach this and, which margins we take. Once the material goes through processing, we generate slides. Every patient's tumor is different. What I show here are and in anonymized fashion, I put tape over that, two different patients' tumors both of, which were transurethral resections of the bladder tumor.

This may end up being the same grade and the same stage but you can tell that the amount of tumor
can be quite different based on how much tumor each patient had. Part of our role is to make sure we look through every slide, every level, go through it in great detail, in this case, transurethral resections. We like to make sure that muscle is present in the bigger tumors. If we can’t find muscle, we make sure the entire specimen has been put through and we document this.

This is in the end what we look at under the microscope. I put here, I’m sure most of you are familiar with microscopes at this point maybe in your treatment but I did put a representative image of one of the microscopes that we do use. They’re a bit fancier, I think than some of what used to be around but essentially, we put the slide up here on the stage and we look through this part up here. These are our objectives and essentially, what we see through here looks like this. I’ve just put some representative microscopic images up here to show you but in this case, this, we would consider normal urothelium. Here’s the lumen of the bladder. This is where the urine collects in the central cavity and there’s a very nice protective umbrella cell layer, urothelial cells below and then, the connective tissue.

We see lots of different morphologies. I just put a few up here.

A lot of what we’ll talk about will be urothelial carcinoma but we don’t forget that there are different subtypes including squamous cell carcinoma, adenocarcinoma and small cell carcinoma. These are very different tumor types each with their own reporting categories and guidelines that we use in our practice.

For those of us who do geopathology or genitourinary, or neurologic pathology, it goes by a few names most typically from one to two years training in the fellowship program that’s focused on that and part of the fellowship training is to really understand what the differences are as we look under the microscope. These differences are ultimately translated into a surgical pathology report.

In this slide, I put up a sample surgical pathology report. The format of it can be a bit different institutions to institutions. In this case, I think what I try to do is capture some of the key elements that people may encounter. Typically, when you look at your sample pathology report, one thing you’ll see is Specimens Received and this comes from the clinical and through the urologist or the radiologist taking the biopsy or the surgery specimen, and it’ll specify bladder tumor.

Sometimes, you may get this and you end up not having a tumor. This one’s a clinical impression that’s made and whether or not it bears out microscopically is a bit of different story. This is a clinical impression and this is what we received and labeled from the clinic. Some places will put pre-operative and post-operative diagnoses. Again, a lot of this comes from the clinical treating physician and depending upon their clinical impression, the imaging, the cystoscopy findings, et cetera.

We know that sometimes things end up not being cancer but we rely a lot on this field of information
and the clinical notes that we received. Typically, then, we'll see a procedure. In this case, a urologist did a cystoscopy to look what was there and then, went on to do transurethral resection of the bladder tumor and this can be abbreviated as well. Some patients may see the abbreviations, sometimes it's just written out. I put this here for clarity.

Part of the report will show the gross examination. We've talked about this in some detail already. This is the description of the material that's received and again, it pretty much gives measurements of what's received, you know, if it's one piece or multiple pieces, what it looked like and this is very important that we know it's been entirely submitted. Not every specimen is entirely submitted. We have some guidelines around that. The majority of biopsies and TURBTs are entirely submitted. Cystectomy specimens, we take the important sections. That includes the margins, depths of invasions, et cetera.

The other part that you'll see is the final diagnosis. In this case, I just put an example; invasive high-grade papillary urothelial carcinoma. So, we tell you what it is, the grade. We specify how deeply it invades and in this case, we put those terms in part of the urologist’s benefit because we have some other terminologies that uses muscularis, so just to be clear, we use this terminology and these sites will do that but not all. It's not a mandated requirement. We specify angiolymphatic invasion because we do know that, that's a risk factor. Also, we'll put a comment. This comment is very important and always emphasize to our urologists that they need to review the comments as well because it may contain very important information.

In this case, this is what we call free text. I like to use this in my reporting. Many locations still do this and I think this frames it in one context. In transurethral resections and cystectomies, we use the free text in our situation together with a CAP synoptic report. CAP is College of American Pathologists. This is one of our regulatory bodies in pathology. They have come up for transurethral resection cystectomies along with most other organism body but not bladder biopsies with a synoptic report. This is essentially a templated report that has all those fields and ensures that all parts of the diagnoses are captured.

One issue we had seen at one point in the past was that not all pathologists were careful for example at reporting whether or not muscularis propria was present. We know that, that's a major indicator of potential progression. Because so many reports lack this and pathologists were not being careful themselves about putting this information, one of our national regulatory bodies put this in place. Most
cancer centers will now require this to be in place for cancer even though it says biopsy is not mandated per se, so a lot of places will not use it for biopsy but it is mandated for transurethral resection of bladder.

In this case, you'll see consistent fields. You should see this in every report and it captures important elements. In this case, it'll capture procedure, tumor type, invasive/non-invasive, histologic type, squamous cell or urothelial carcinoma. We allow for variant diagnoses, for staging. For squamous cell carcinoma, small cell, et cetera. Especially epithelial lesions with a grade, mostly it's high-grade, whether or not muscularis propria is present meaning, do we have adequate material, whether to not vascular invasion is present and how deeply did the tumor invade. This is very helpful to the urologist in determining the next steps of treatment.

To highlight a few important thing for patients to understand about pathology report. I know that when you look at it as a patient, it can be a bit overwhelming and it's a lot, a lot of information. It's clear based on that study that there could be a room to develop resources to help patients better understand this. It is important to know that the data that's entered into the report is required by a number of regulatory bodies and the language is very specific. Historically, this is less of a problem because these reports were primarily viewed by the urologist or the oncologist.

Historically, a lot of medical centers didn't really worry so much about whether the terminology was clear or not. Now that we have electronic charts and medical records, patients also have the opportunity to see these reports. Looking at a report without someone to explain it to you like your urologist, oncologist or pathologist, we understand it can be very difficult to interpret and understand, and I think I did want to point out. Pathology diagnostics are basically interpretations of pictures and images that we see.

```
Important Things to Understand About Pathology Reports

- Data entered into the report is required by a number of regulatory bodies and the language is specific
- Historically, these reports were primarily viewed by the treating physician (urologist), but with electronic charts patients also see these – thus, the terminology may be difficult to interpret in isolation
- The diagnosis is often subjective, despite diagnostic descriptions for each entity – use of the diagnosis is never in isolation, but needs to be supported by full clinical evaluation to be sure everything matches the clinical picture for appropriate treatment
```

For every patient, this is very important. The diagnosis is often subjective. Despite the fact that we have books and guidelines, and trainings to say these are very specific guidelines for some of the diagnoses, the fact that most biopsy TUR cystectomy specimen don't read the book. In the end, it's based somewhat on oncologist experience, clinical history, imaging, et cetera and so, there's some room for error in this. It's important as a patient to understand that the diagnosis is not always and often not a black and white diagnosis. It is put clinically into the context of clinical evaluation, imaging, et cetera.

I just wanted to touch briefly on grading and staging because I do know that some of the participants in the webinar did have some questions and this isn't meant to be a definitive tutorial on grading and staging. It takes people about a year in sub-specialty training to learn this and these criteria change over time. For those of you with a pathology report, I am hoping that this can provide a bit of a guideline in
how to understand and put your report in context.

To start off with, we'll talk about the grading of bladder cancer. To grade bladder cancer, in this case, we don't worry about invasion or non-invasion. In this case, we look at the cells themselves and we say, "Well, how abnormal are the cells?" We look at things, and I'll show you a picture in the next slide, so that you could put this in context. We look at features such as nuclear atypia, disorganizational organization. Words like hypochromasia, which just means how dark a cell or nucleus is, the size of the nuclei, the number of dividing cells, location, and mycotic figures.

Some of the things I'm saying, you may have seen in some of your reports that you've gotten back. A lot of times, this is meant to inform the urologist, the oncologist, the pathologist especially in more difficult cases what we're using to try to make our decision because like I said, these can be subjective calls. The longer note is, as a rough guideline, this isn't cut in stone. The longer note is the more complex your assessment probably could be. We'll even encourage the urologist, the longer the note maybe you should pick up the phone and call. We call in reverse. That typically means we're explaining why we got to a decision that we made.

We'll say for non-invasive, the urothelial carcinoma we typically will say low-grade and high-grade. Invasive carcinomas are predominantly high-grade. It's rare to never that you would have a low-grade in invasive carcinoma. This is important from a clinical end because we know low-grade can frequently recur. It's about 10 to 15% of patients could potentially progress. However, if you have a high-grade diagnosis, there's a much higher likelihood of subsequent invasion if the disease persists.

Some lower entities that you may see are papilloma and PUNLMP. These are a bit more indolent. They're on the lower scale below low-grade. Here's a slide that shows some example of grading. On the left hand of your screen is a low-grade, non-invasive papillary urothelial carcinoma. On the right side is a high-grade, non-invasive papillary urothelial carcinoma. I picked two cases where it's pretty clear cut differences between low and high-grade. You could tell it might be a little bit challenging because you have all these cells falling off, sometimes it's not well-preserved, sometimes it's crushed a little bit that we get a lot of nuclear features or architectures.

In this case, when we talk about a nucleus, we talk about these little circles where all the DNA is and when we talk about organization, we talk about how they're arranged up and down within the papillae and when you compare low-grade to a high-grade, you just see here nuclei are much, much bigger. They're darker or hyperchromatic. You could tell that the nuclei are not evenly arranged but they're scattered throughout. These are some criteria a pathologist will use to make a diagnosis.
The problem is, not all of these cases are picture-perfect cases meaning, sometimes, there could be a fixation changes, small biopsies, cautery artifact. Some issues that can really lead to challenging an interpretation. I will say that despite the fact that we do, you know, all of us get together periodically to revise criteria. Just recently I’ve been involved in rewriting the World Health Organization's guidelines as well as AJCC staging guidelines. I will tell you that these are very objective criteria that go into it.

We try to come up with some consensus document to help people. Again, the clinical impression is very, very important. For the most part, we don’t have good markers to help us objectively categorize some lesions. A good criteria then for example for prostate cancer where we have grade markers for basal cells. We really don’t have that in bladder or urothelial cancer. We always recommend that the urologist take this report into account with the clinical findings and especially if there’s some difference where we think there’s a cancer but the urologist doesn’t. That’s when there should be a conversation or biopsies performed.

It’s typically not proper clinical care for a urologist to just jump and act on a pathology report. There's typically much more of that that goes into the decision making. If you feel that, maybe you're not getting enough focus on what the pathology is or if there’s some question that you’re perceiving with the pathology report. That’s really when you need to ask to talk to someone as Matt had pointed out.

To briefly move through staging of bladder wall, when we talk about staging, you’ll see a pP stage, pathologic P stage. You will also a cP stage, which is the clinical stage. That essentially tries to gauge how much in a non-invasive tumor, where it is on the wall. Non-invasive tumors will set up here and be confined to the lumen whereas invasive tumors will move through the lamina propria. It’ll move in to the muscularis propria to detrusor muscle there and the perivascular fat, et cetera. It essentially gauges the depth of invasion through here.

This is important for treatment in transurethral resection even though we don’t technically call it staging. We give a description and in prognosis in cystectomy specimen. Just to show you some examples, this is moving around clockwise, non-invasive disease, this is the papillary lesion, non-invasive disease, this is the papillary lesion, non-invasive confinement. I just showed a high magnification because you don’t really see the base. We move on to lamina propria invasion where here, the T1 disease where you could see that here’s the sources and it’s in this layer of the bladder wall.

As it invades deeper, it starts to get into the muscle and you can see here tumors surrounding the muscle and it ultimately can go to lymph nodes and you can see tumor present in the background with the lymphocytes. Those are the factors that we put and include in our reports as we generate them. Similar with grading challenges, there are challenges with staging as well. As I’m playing out before, biopsy and transurethral resection specimen, we do not assign a pT stage because this, based on guidelines is reserved only for major resection assessments, so for a cystectomy for example.
After we review the data and this was an area that I presented to AJCC and has now gained some traction, we have now recommended that there'd be some degree of measurement of the amount of invasion on tumors, on biopsy, and TURs that are in the lamina propria. We think that this may have an important piece of information for whether or not a tumor is more likely to progress. You will start to see this in future pathology reports more and more.

We're also very careful to assess for detrusor muscle, so if it's not present, we cannot say whether or not there is muscle invasion. In almost all cases, there should be a re-staging TUR but for sure, in cases in which muscularis propria in the detrusor muscle is not present, that definitely needs to happen. Sometimes, due to the pattern of tumor invasion, there may be a question of whether or not muscle bundle that's present are actually detrusor muscle. Again, in these cases you'll see a very long note. In these cases, always make sure to ask your urologist to go to for more detail about what's happening.

Some other diagnostic terms patients may see and I realize this is not a comprehensive list, but some of these terms you may see on cystectomy. You may see a description of margins or you should see a description of margins. This will be on a template and maybe in a free text. This includes ureter, urethra, soft tissue, margins and sometimes, especially with the ureter, there may be frozen sections done on that and we do that while the surgery is going on as a preliminary diagnosis to help the urologist decide to take more or not.

Other Diagnostic Terms Patients May See

- **Margins** = on cystectomy specimens includes ureters, urethra, soft tissue; indicates if any disease is left behind
- **Angiolympathic/lymphovascular invasion** = describes if tumor is in a blood vessel or lymphatic – thought to be a worse disease course indicator
- **Non-urothelial cancer** = may include squamous cell carcinoma, adenocarcinoma, or small cell carcinoma – these often behave differently and may have other treatment implications

You'll see a description of angiolympathic invasion or lymphovascular, they're the same thing. This describes if the tumor's in a blood vessel or lymphatic and it's potentially the worse disease indicator although some studies are controversial. You'll also see, depending on your disease status if you have squamous cell carcinoma, adenocarcinoma, or small cell carcinoma, you may see a little bit of a different format or report with those just because they are a different disease processes.

If you have cancer in a non-bladder location and this can happen because often, patients with disease at one site may develop disease at another site, not always but sometimes. This will include the ureter, the renal pelvis, which is also kidney, urethra or prostate. Staging is different at each location. Especially in the upper tract, the sampling is much more difficult. If you end up being potentially upgraded or upstaged in the upper tract, that can happen because these are very difficult locations to access.

When you go back and look at the number of cases that are upgraded or upstaged, it's actually a fairly high percentage just because the scope can't get up the biopsy on all these different sites that may have the worst tumor. These are also usually small challenging biopsies, often fresh artifacts. This is a very difficult area in diagnosis for a lot of people. Again, usually the urologist is very careful to do a clinical correlation to make sure that the diagnosis is confirmed.

To wrap up, I just wanted to spend the last two slides on pathology re-review, which in my mind, the
more eyes on assessment, the better especially before you have a major surgery. That's really the time that you need to do it. There are a number of guidelines here on this. What we do is if a patient comes to us or it's an existing patient at my institution, I actually will see a patient in my office, in the urology office if requested. We just sit down. We can look at the tumor together. We can talk about it. I think patients can feel more certainty in their diagnosis and were very clear if there are areas that are difficult or subjective when we talk about what's in the note.

The problem is this isn't a highly reimbursable process and so, even though I think, some of us think it's best for patient care due to time and money constraints at hospitals, this may not be done but I think it's by far the most integrated. The other three options, we do contest these reviews by in-house sub-specialists if they're available. This may depend where you are. This is more likely at larger medical centers but I think you got a couple of eyes on it. If a patient transfers care from an outside location to our hospital, the national guidelines around this by a number of regulatory bodies is that this is a requirement.

If you decide to switch from institution A to institution B, your urologist or oncologist at institution B should be requesting a pathology re-review to verify the diagnosis. It's important because as I put here, up to 40% bladder cancer diagnosis are changed on re-review, changed in a small way or in a big way, but there's a change. Sometimes, cancer is not cancer and so, we always call a urologist if they've done a surgery without having re-reviewed the prior material because we view that as a poor indicator of patient quality of care.

There are guidelines around this and you should strongly request this if you change institutions. There's also advertisements online for second opinion diagnosis. It's directed towards patients or pathologists. With this, I just wanted to highlight a few caveats. This is my last slide. It's important to understand a few points because I know when I go online on the internet, there are a lot of people advertising for you to send material to them. I think it's important to recognize that all these diagnoses are subjective.

What you can end up with is one opinion versus another. Sometimes with expert in the field. I think, I would never listen to one person who says, "I'm always right," and "I'm the expert." These are subjective and groups of us get together to debate and finalize some of the guidelines. There are many places who advertise themselves as experts but they may not be. High volume centers that do hundreds of cases a day, it's physically impossible for the person signing out to review every single slide in all that material and they often do not have the image in their clinical charts. I would be very careful because like I said, nothing can be done without the clinical impression.

This is the concern of mine that I have seen in practice. There is some financial incentives to places that advertise for second opinions. Here, you know, because these two things bother me quite a bit, for
patients who do want to come here, I, for example have not been charging and I take time and meet with the patients. I do that because I support BCAN and I think that's a good practice. We should start thinking about adopting more broadly. I typically do not go online to advertise anything but I do take care of patients when they come. I think these are all questions we should be aware of.

We should also be aware that often, second opinions may not be accountable from a medico-legal perspective. It's kind of up to you who you decide as a consultant or pathologist who, you know, someone may ask to be a second opinion consultant. It doesn't mean that they may be accountable for that diagnosis. Ultimately, not to scare you, I think second opinions are wonderful. I think they're important. I think it's important for you to be aware that one opinion versus another can sometimes happen.

It doesn't mean that one person's bad or good. I think that means you have a challenging case and I think that's where you're getting your urologist and you start to integrate, have your urologist integrate the pathologist into the clinical care that's going on and really get a dialogue going, so that you could get the best care for yourself, for your family member. With that, I wanted to thank you all again. I hope that this was helpful and I wanted to thank Matt for bringing up an important area that I think needs more work. Thank you again to BCAN.

---

Caveats with Second Opinion Review

- Given that diagnoses are often somewhat subjective, this results in "one opinion versus another"
- Many places advertise themselves as experts
- High-volume centers may not actually review all the material and often do not have the imaging or clinical charts to tie in to the patient clinical findings ("diagnosis in a vacuum")
- Places that advertise second opinions often receive financial incentive to the pathologist or department (we have not been individually charging patients who have questions and require re-review)
- Second opinions may not be accountable from a medico-legal perspective, so there is always a question of accountability
- Better integration of the pathologist in in-house urology/oncology clinics and in-house subspecialty peer pathologists may be a better model to render reliable, team-based diagnoses

---

BCAN would like to thank

Genentech
A Member of the Roche Group

EMD Serono

MERCK

Be well

for their support

---

11 Understanding Bladder Cancer Pathology | BCAN Patient Insight Webinar 2017