



What's the Deal with Carcinoma in Situ (CIS) and Why Does It Matter?

Guest Speaker:

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Patricia Rios:

I want to welcome all of you to BCANs, or the Bladder Cancer Advocacy Network, Patient Insight Webinar series. Again, my name is Patricia Rios, I am the director of education advocacy here at BCAN and your host for today's webinar on What's the Deal with Carcinoma in Situ, and Why Does it Matter? Carcinoma in situ or CIS is a type of bladder cancer that can be tricky to understand. It doesn't form a lump or tumor you can see, it grows flat along the bladder lining, which makes it harder to detect and treat. Doctors sometimes disagree on how best to diagnose and manage CIS or carcinoma in situ, which can be confusing for patients. In this webinar, Dr. Pietzak and Dr. Matoso will explain what carcinoma in situ or CIS is, and what researchers are discovering about how CIS develops, and how these insights are shaping treatment approaches.

I would like to begin by introducing our phenomenal speakers for today. I will first introduce Dr. Pietzak, Dr. Eugene Pietzak is a urologic oncologist at Memorial Sloan Kettering Cancer Center in New York, who specializes in the surgical treatment of bladder cancer and upper tract urothelial carcinoma. Dr. Pietzak is also the principal investigator for multiple investigator-initiated clinical trials for patients with non-muscle invasive bladder cancer.


Joining Dr. Pietzak is Dr. Matoso, who is a professor of pathology, urology, and oncology at the John Hopkins University School of Medicine, and serves as director of the Urologic Pathology Division and the Genitourinary Pathology Fellowship Program. He's a leader of the Johns Hopkins Urologic Pathology Consult Service, one of the largest in the world. Dr. Matoso also authored more than 170 peer reviewed publications, contributed to the World Health Organization classification of tumors, and is an internationally recognized speaker and educator. So at this moment I am going to hand over the screen to our presenters, we will first hear from Dr. Matoso, and directly after that we'll hear from Dr. Pietzak.

Dr. Andres Matoso:

So, thank you so much for the introduction and the opportunity to be here today to talk about this very important topic, CIS.

Dr. Andres Matoso:

The objectives of my presentation, I'm a pathologist, even though I have appointments in urology and oncology my main work is in pathology. So, my idea today is to show you what CIS is and why is it different than other types of cancer, how does it differ and how does it grow differently than other types of bladder cancer? And why is CIS difficult to diagnose from the pathology point of view? So the goal of all this is to help patients understand what CIS is, and this will help you better understand your care and all the different steps that you have to go through


Objectives 

- **By the end of this lecture, patients will be able to:**
- **Understand what carcinoma in situ (CIS) of the bladder is**, and how it differs from other types of bladder cancer in terms of growth pattern and behavior.
- **Recognize how CIS is different from other early or precancerous changes in the bladder lining**, including why it may not form a visible mass or tumor.
- **Appreciate why CIS can be difficult to diagnose**, including the limitations of biopsies, microscopic appearance, and why expert pathology review is sometimes needed.
- **Understanding CIS helps you understand your care!**

Dr. Andres Matoso:


to manage this disease.

Understand what carcinoma in situ (CIS) of the bladder is

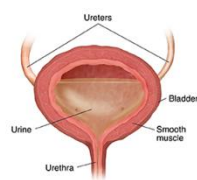


Dr. Andres Matoso:

So first, introduction about the bladder, most of you probably already know this because it is your disease or your loved one's disease so you probably have informed yourself. But the bladder has different layers, and what we're going to be talking about is the more most inner layer of the bladder, which is the urothelium. This is the lining that covers the bladder and protects the urine to be kept in place. And this is where the cancer starts, in that lining.

What does the bladder wall look like? 


- The bladder is lined by a thin inner layer called the **urothelium**
- This lining protects the bladder from urine
- Most bladder cancers start in this lining



Dr. Andres Matoso:

So it happens, bladder cancer happens when that lining or that urothelium grows out of control. But, it can form tumors, lumps, as in any cancer. But the difference with CIS is that that tumor is flat and it sort of merges with the normal lining of the mucosa, so it's hard to see.

Bladder cancer basics



- Bladder cancer happens when lining cells grow **out of control**
- Some cancers grow as **lumps or tumors**
- Others grow in a **flat, spread-out pattern**


Dr. Andres Matoso:

And I'm going to show you some examples.

But by definition, CIS is high-grade cancer. The cytology or the features of those cells are of high-grade, and I'm going to show you why. And these tumor cells are confined to that lining, it's as if they were hiding or mimicking the normal cells. They grow in a flat way, they don't form a lump or a tumor,

and it's considered aggressive. It's considered aggressive because it has higher chances of invading than the papillary tumors or the other type of cancer. Also, when it invades sometimes it's not seen because it doesn't form a lump.

What Is Carcinoma in Situ (CIS)?




- **CIS is a high-grade cancer limited to the lining:**
- CIS is made of **cancer cells**
- These cells are:
 - Confined to the bladder lining
 - Flat, not forming a lump
 - CIS is considered aggressive, even though it is superficial

Dr. Andres Matoso:

So, as I was mentioning, it grows along the surface like a rash, it's similar to a rash on the skin. But the difference with the rash is that this is not visible, when the urologist goes inside the bladder they can, often they cannot see. All that they see is a little bit reddish area if they are lucky to see that, but it's not a very sensitive feature so it's not always present. It can also involve large areas of the bladder lining, and in multiple different large sites in a discontinuous way. It can also

How CIS Grows: Flat and Hidden




- Spreads **along the surface**, like a rash
- Does **not** form a visible tumor
- Can involve large areas of bladder lining
- Can involve the prostatic urethra and colonize prostate ducts

line the urothelium of the urethra that goes into the prostate and grow into the prostatic ducts in a way that is impossible to see with a cystoscopy.

So all these are the natural way the tumor grows and why is it difficult to, to diagnose.

Dr. Andres Matoso:

So here is a table to summarize those features, CIS versus a typical bladder tumor that makes a lump or a papillary tumor. And the shape, the CIS is flat, while the tumor makes a mass, it can bleed, it has a papillary structure. The CIS is difficult to be seen, while the tumor can be easily be seen. CIS is always high-grade, the tumors can be low or high-grade. And the risk of progression with CIS is high, while the typical bladder tumor can be variable based on the grade. But CIS is always, by definition, high-grade.

How CIS Is Different from Other Bladder Cancers 

Feature	CIS	Typical Bladder Tumor
Shape	Flat	Raised mass
Visibility	Hard to see	Easy to see
Grade	High-grade	Low or high
Risk	Higher risk of progression	Variable

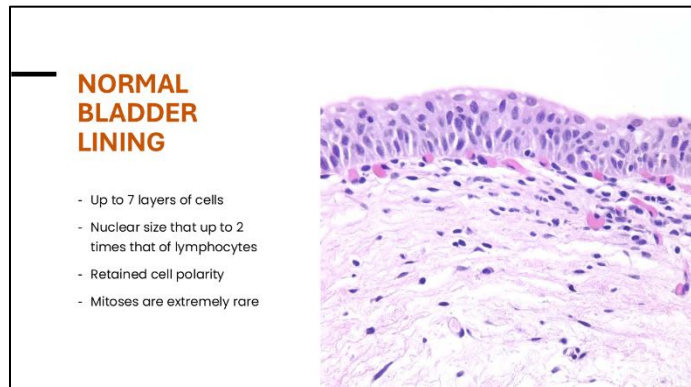
Dr. Andres Matoso:

Now how is it diagnosed? It always requires tissue examination.



Dr. Andres Matoso:

So first I'm going to describe, this is a histologic view of a normal bladder mucosa where you see the lining, the urothelium has up to seven layers of cells. And the nuclear size of those epithelial cells, these are the nuclei, are small. When we compare it to a lymphocyte, this is a lymphocyte, lymphocyte is an immune cell, these nuclei are two times the size of those

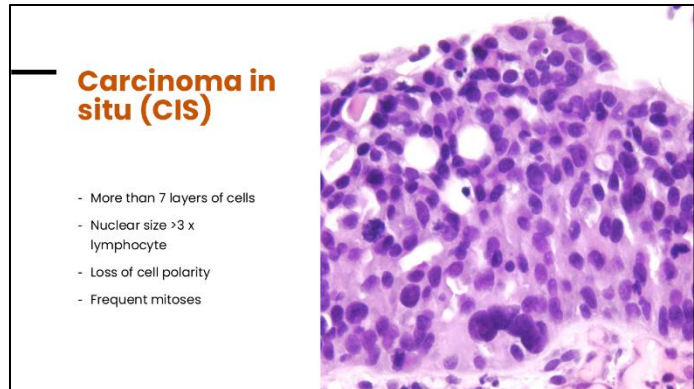


lymphocytes, but not larger. They also have a polarity. Polarity means that these cells recognize where the floor is and where the sky is. So for them they have that orientation that is standing up because they have sort of, supposedly feet underneath and then the head and the body on top. So that is what I refer by polarity, that the cells know where the base is and where the roof is. So they have that orientation, and that's the normal orientation, normal polarity of those cells.

There are some cells on top that are called umbrella cells. Those are also normal, and they cover the surface. And the role of those umbrella cells is to form a tight junction on the surface to avoid the urine to leak through the lining or the urothelium.

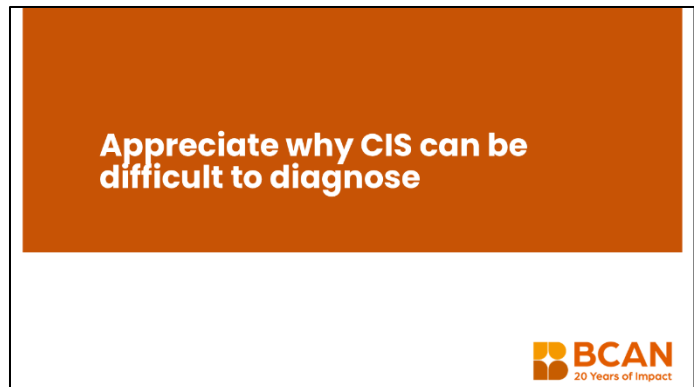
Dr. Andres Matoso:

Now when we have CIS you can see now that we have way more than seven layers of cells, all these are nuclei. Also, the size is huge. They have more than three times the size of lymphocytes. They have frequent mitosis, these are mitosis because they're replicating a lot, they're growing out of control. The polarity is lost. Some of these cells are very round, some of them are facing sideways. They do not respect each other's boundaries, their nuclei overlap, and they grow so fast that they crawl all over each other, and then the frequent mitosis. So this is a high-grade cancer that is lining now the bladder mucosa, and that's CIS.



Dr. Andres Matoso:

Now why is it difficult to diagnose? Because the pictures I showed you, it seems very easy to recognize those two separate entities.



Dr. Andres Matoso:

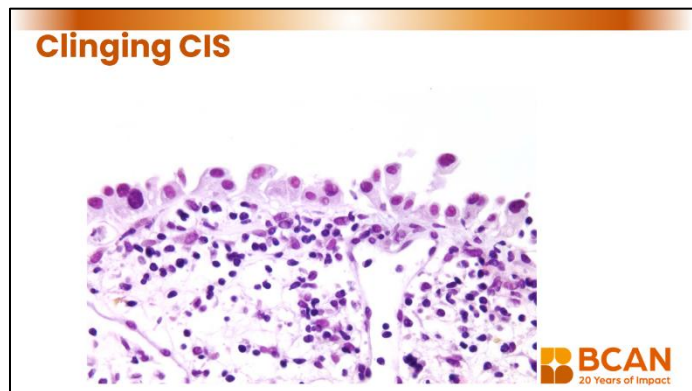
Well one of the properties of CIS is that those cells become discohesive, meaning that they can become very loose with one another. Instead of staying attached to their neighbors they lose that attachment. That is a property that cancer cells acquire so that they can move, and migrate, and do their job of invading other tissues. Now when that happens the cells can

completely detach from the bladder mucosa. And as you can see here, you have the base of the urothelium, but there is no urothelium so because there's extensive denudation of that bladder mucosa. This patient had presented with hematuria, pain in the bladder, they go and do a biopsy, and there are no cells. So when we have this finding we cannot make a definitive diagnosis, but we suggest that denudation could be a sign that there is CIS.



Dr. Andres Matoso:

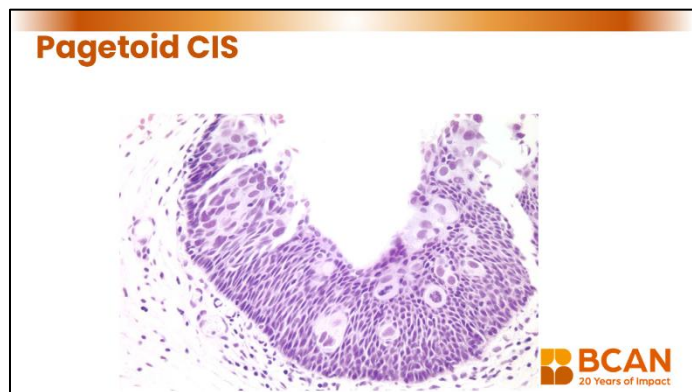
This is an example of what's called clinging CIS. In this case, instead of all the cells being shedded off, because of this cohesiveness we have still one single layer of cells at the base. Now when this happens sometimes it's difficult to appreciate the atypia or the nuclear size of these cells, and making a diagnosis can become difficult for general pathologists that are not used to handling this kind of a difficult cases on a daily basis.



Dr. Andres Matoso:

Sometimes the bladder, the normal cells will repopulate the lining, as you see here with the smaller cells, and then you have CIS in a pagetoid manner. So some of the cells are CIS, but the majority of them are not CIS.

So this can also create a lot of uncertainty when these cells are not that abundant, when we have only a few, and they might be more difficult to arrive at a diagnosis that is very serious. So we do not make the diagnosis unless we are 100%



sure. This case is for illustration purposes, and it's easy because you even have mitosis, but you can see how the cells of CIS compared to the normal urothelial cells, how much bigger they are. And also they are atypical and they're round, so they have lost their polarity.

Dr. Andres Matoso:

Now this is perhaps the most difficult of the situation, what is called dysplasia.

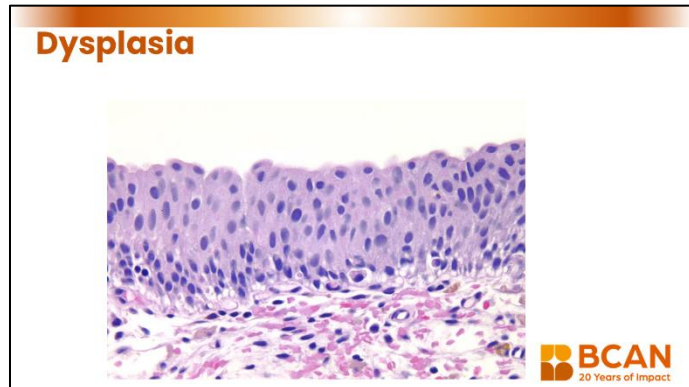
Dysplasia is a urothelium that is abnormal because it has some cytologic atypia, but it's not as overt as in the cases that I showed you before of CIS. So these are sometimes considered precursors of low-grade papillary urothelial carcinoma. It's also a flat lesion, it's also atypical to be

flagged, but it's not atypical enough to make a diagnosis of CIS. And why we do not, we want to prevent over calling CIS in all the patients. So once we make a diagnosis of CIS we like to feel 100% comfortable because we know it has a significant implications for the patient. So when it looks atypical but it's not as severe a CIS, we call it dysplasia.

What do they do? The urologist, what do they do with dysplasia? If the patient already has a diagnosis of CIS before they know that it could be coming back. If it is a first-time diagnosis they will follow up that patient with a repeat cystoscopy, with urine cytology in order to confirm the diagnosis of CIS when that is enough to be diagnosed.


Dr. Andres Matoso:

So here is the management that I was mentioning in someone without a history of CIS. With a history of CIS this indicates that the disease is coming back. In someone who does not have CIS and is a de novo diagnosis of dysplasia, this is considered a precursor of low-grade papillary urothelial carcinoma. The patient is followed up for the development of cancer, so they're followed more closely in a potential conversion to CIS.



Management of Dysplasia

- In someone with h/o of CIS, indicates the disease is recurring
- In someone with de novo diagnosis of dysplasia, it is considered a precursor of low grade papillary urothelial carcinoma.
- Patients with de novo diagnosis of dysplasia are often followed more closely for potential conversion to CIS




Dr. Andres Matoso:

Now another difficulty for us is when the urothelium shows reactive changes. Reactive changes means the urothelium is trying to regenerate and fight infection or a source of inflammation.

Reactive urothelium


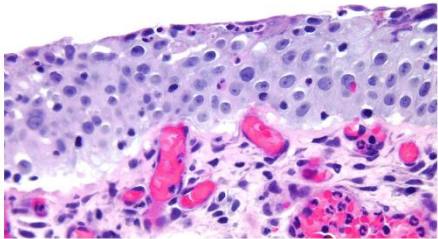
- Acute or chronically inflamed urothelium
- Vesicular uniformly enlarged nuclei with central prominent nucleoli
- Mitotic figures may be common
- History of instrumentation, infection, stones, therapy



Dr. Andres Matoso:

And the problem is that the cells become large, but they have associated inflammatory cells. So here we have several of the features of CIS, the nuclei are large, the polarity is lost, and the thickness could be increased, but there is associated inflammation, you can see neutrophils here. And this needs to be recognized, that inflammation, because some of the

Reactive urothelium




nuclear changes could be secondary to this inflammation. So when we have atypia to the point that we think it could be CIS but there is associated inflammation, our threshold for calling it CIS significantly increases. So we want to see very marked atypia. So some of these patients might have already CIS, but the presence of inflammation prevents us from completely excluding a reactive process secondary to that inflammation. And therefore, in those cases, the patient needs to get a repeat biopsy after they have treated that inflammation, either with antibiotics or other measures.

Dr. Andres Matoso:

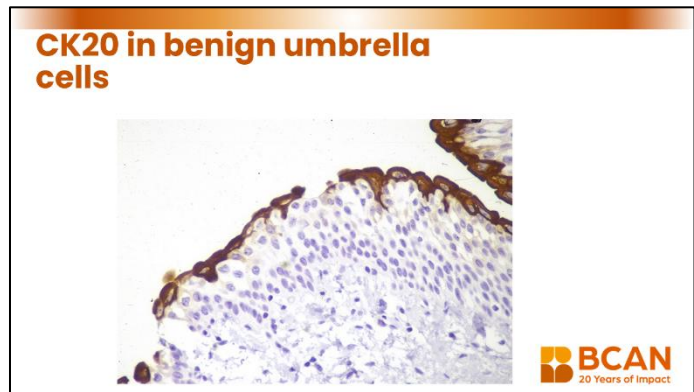
We use immunohistochemistry to diagnose CIS, and some of the markers are mentioned here like CK20 or Cytokeratin 20 and P53. There are different patterns of stain that can aid in the diagnosis of CIS.

	<u>CK20</u>	<u>P53</u>
<u>Normal/Reactive</u>	Umbrella cell	None
<u>CIS</u>	All layers	Frequent



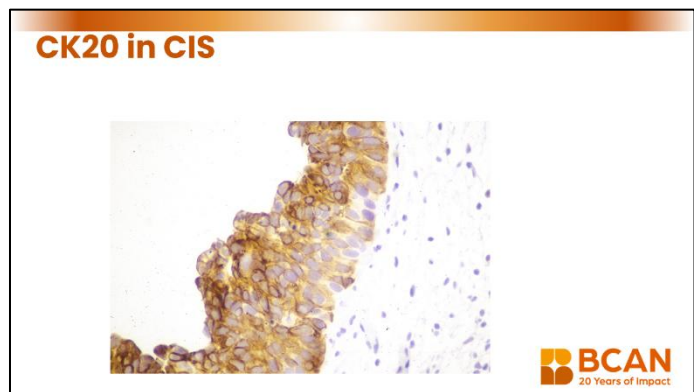
Dr. Andres Matoso:

This is Cytokeratin 20 normally stains the umbrella cells but not the rest of the urothelium. And this is a normal pattern of CK20.



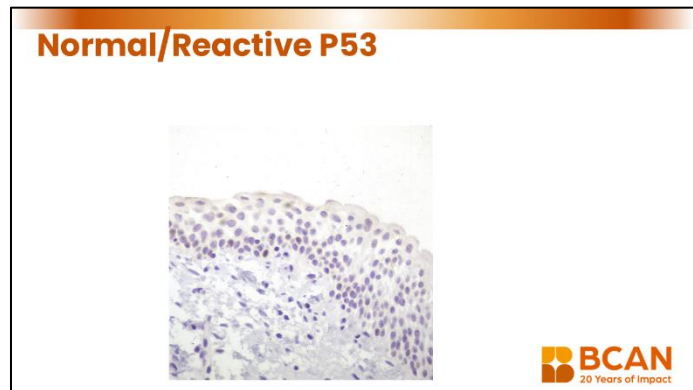
Dr. Andres Matoso:

While in CIS, Cytokeratin 20 stains the full thickness. This is a finding that is present in approximately 80% of the cases of CIS.



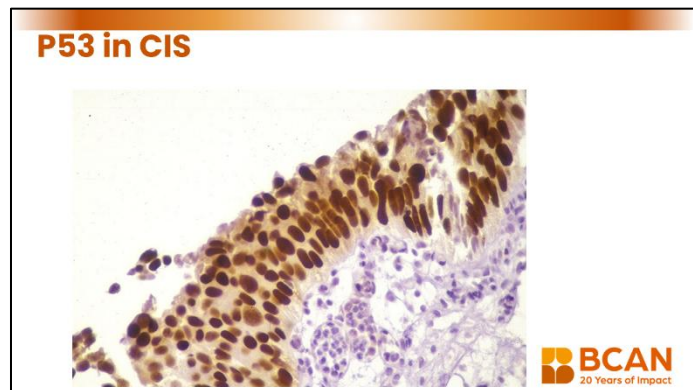
Dr. Andres Matoso:

We can also use P53, which is a tumor suppressor protein. P53 normally is expressed in low levels in the nuclei of cells, but when there is a mutation, which is one of the most frequent genetic alterations of high-grade urothelial carcinoma, then P53 becomes over expressed in the cell and accumulates in the nucleus, but it's non-functional because it's mutant.



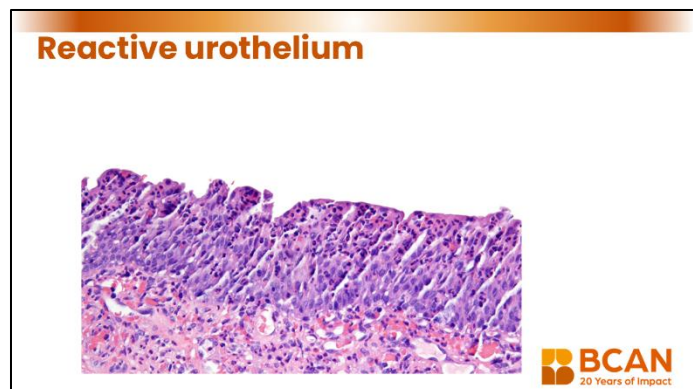
Dr. Andres Matoso:

And then that leads to over expression of P53, and you see here in brown how those large nuclei over express P53. So in those cases where we are dealing with reactive versus CIS, immunohistochemistry for Cytokeratin 20 or P53 could help in supporting a diagnosis of CIS.



Dr. Andres Matoso:

Here is an example of a very inflamed urothelium. It looks atypical, the nuclei are angry, but there is a lot of inflammatory cells so we're not going to make a diagnosis of CIS in that setting.



Dr. Andres Matoso:

When we do P53 we see certain degree of expression, but it's less than the one that showed you with CIS. But this could be also difficult to interpret because there is significant expression of P53 in those cells.

