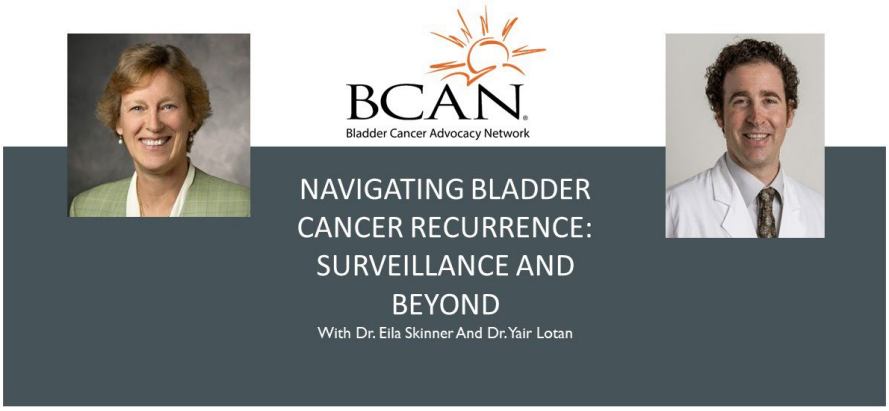
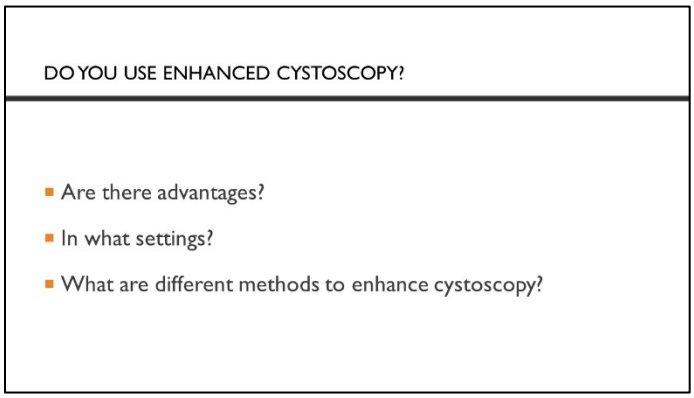
PART 2

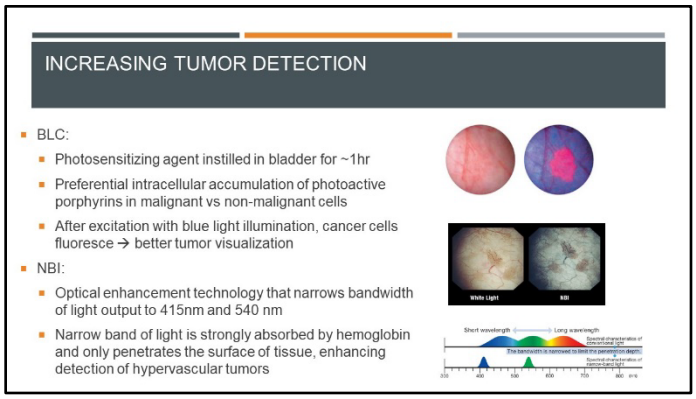


Dr. Yair Lotan:



So as we mentioned earlier, some of the tumors, especially carcinoma in situ can look like red patches or just not be visible with normal view. And one of the problems when you give drugs like BCG, which cause a lot of inflammation, is that you do end up with red patches and then you don't know if it's cancer or if it's just inflammation. And so many people will try to use enhanced cystoscopy. There are a couple of different modalities to do that to try to identify cancers that are not well seen with typical white light cystoscopy. And so there's two main strategies. One is called blue light cystoscopy, and for blue light cystoscopy you have to put an agent in the bladder. It's called Cysview, but essentially it's kind of like a nutrient that cancer cells selectively take into the cell. The normal cells usually are not bringing in. And when this photoactive substance gets into the cell, when you shine a blue light on it looks pink. And this is sort of a classic picture.

Dr. Yair Lotan:

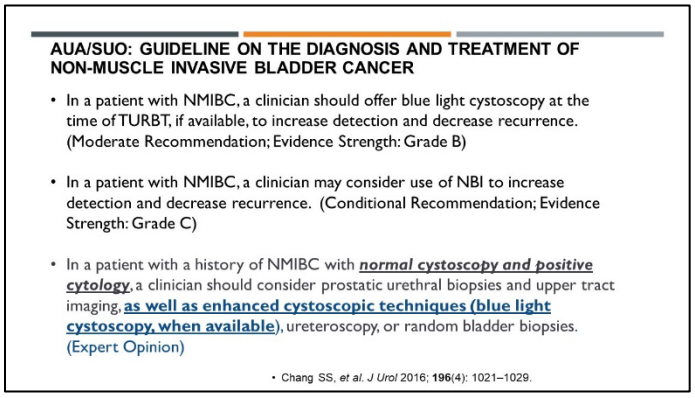


It doesn't always look quite that nicely differentiated in the operating room, but many times in surgery if you use this you can identify some areas that you might've missed otherwise. And it seems to improve detection of carcinoma in situ (CIS) by about 30% and sometimes can help you find some additional papillary tumors as well. And there are multiple studies that have looked at it. And so quite a few centers have this in the hospital for surgery and there's a handful of places that also have it in clinic, but the main manufacturer right now is not really selling the

scopes for it. So it's still pretty limited who can do it in the clinic setting. The other option is narrowband imaging. It's basically a way of looking at wavelengths of light that will make blood vessels look green. And since cancers attract blood vessels, if you look for the areas that are getting more blood, you might see some additional tumors that you might miss. And so this is kind of an example and you can see the tumors are a little bit more, a little easier to see.

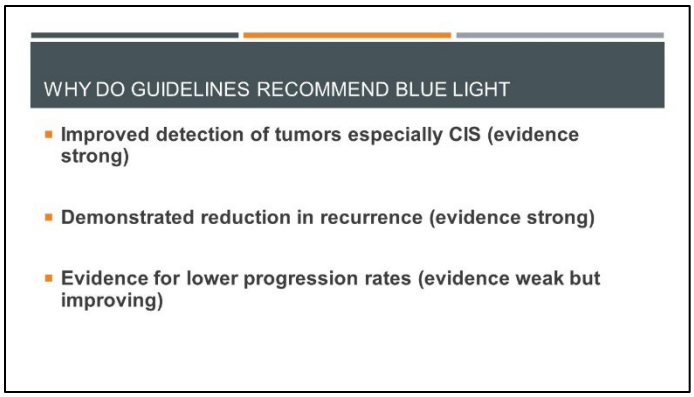
I think you can see two of them quite well. But one of them is a little pale at the bottom left and you can sort of see it better with a narrowband imaging. And there are some studies that have shown that this improves detection. The good news is it comes on a lot of scopes automatically and you don't have to instill something in the bladder ahead of time, but not every scope has it. Not everybody uses it who has these scopes.

Dr. Yair Lotan:



So we have guidelines that kind of help us try to decide on how to best approach patients. And basically there are several settings where if you have blue light and you're concerned about recurrence or for example, sometimes we don't see a cancer but we do a urine wash and it shows cancer cells and we don't know where did we miss it. So then we say, well, we better do a scan of the kidneys to make sure it's not cancer in the lining of the kidneys, but maybe we should use enhanced cystoscopy in the bladder to see if we can find some abnormal patches that we might've missed with white light.

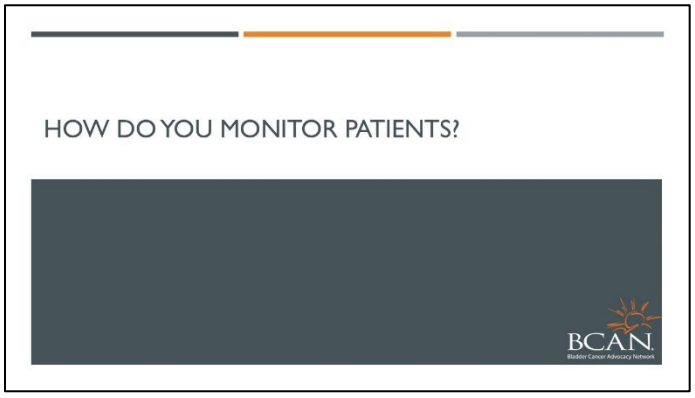
Dr. Yair Lotan:



And so as I mentioned, there's good data that shows that it will improve detection of carcinoma in situ and can reduce recurrence of cancers in the early phase because if you find them at the time of resection, you get rid of them and then you don't see them three or six months later. There's some data that is looking to see if it reduces progression, but these events are really pretty rare, so the data is not very strong as of yet.

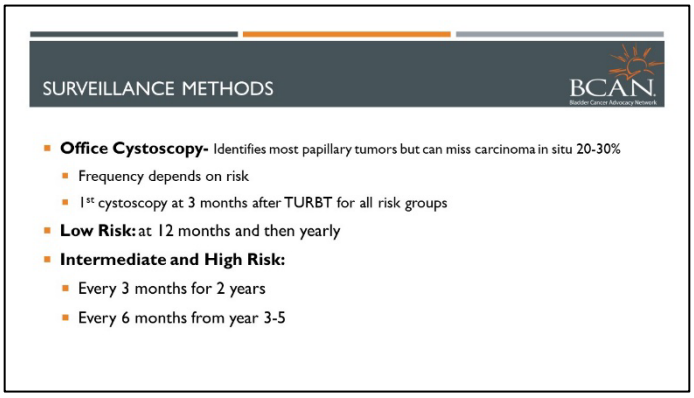
PART 2

Dr. Yair Lotan:



So how often should we monitor patients? We mentioned how frequently this recurs, so how quickly should we look in the bladder for patients?

Dr. Yair Lotan:

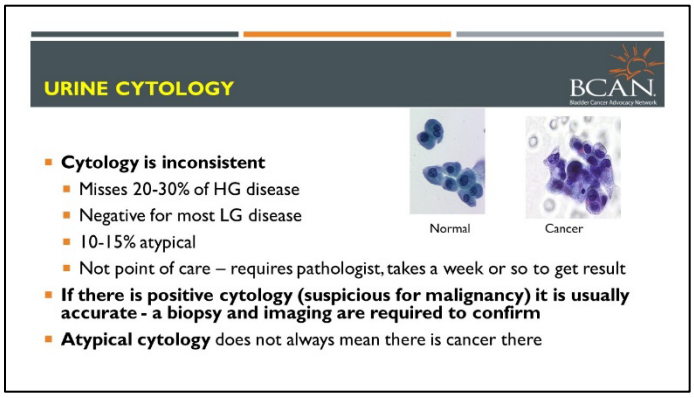


So how do we do it? Well, first of all, we look the same way. We found it in the first place in the office, look around and it's important. The most important time to look is actually at three months. As Dr. Skinner mentioned earlier, if you're disease free for several years, you're much less likely to have a recurrence over time than right off the bat.

And right off the bat, at three months you really need to make sure, especially if you gave somebody six weeks of chemotherapy or BCG, you want to make sure they responded and you want to make sure you're not missing patients who have a high rate of occurrences. Now, if the patient was low risk and that was a patient who had maybe one small tumor and at three months you don't see anything, you may not need to look again for nine to 12 months and then once a year afterwards. But for intermediate and high risk patients, we usually look every three months in the first two years and then every six months until year five. For some intermediate risk patients, we might do it every six months in the second year as well, depends on how they became intermediate risk. As I mentioned, there's a lot of variety. So you could have started off with two small tumors and been intermediate risk and not recur for a long time. So there's a little bit of subjectivity there, but certainly we look quite a bit more often for those patients.

PART 2

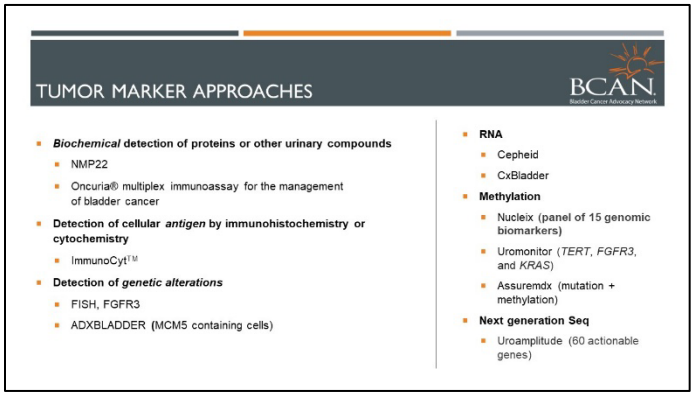
Dr. Yair Lotan:



So cytology is something that we commonly will do at the time we do cystoscopy, which is to collect some urine and send it to the pathologist to look under a microscope. It's much better for high grade disease than it is for low grade disease because low grade disease, the cells by themselves look very similar to normal bladder cells. And so cytology is really not that useful for patients with low grade disease. Some people will use it because they want to find those rare cases that patients progress to high grade disease, but it's not uniform. But for high grade disease, it definitely will help catch those patients who might be missed, even though unfortunately it's still wrong about 20 to 30% of the time. The one downside of it is that we might look in the bladder, tell you everything looks great, we collect urine. Five days later the pathologist sends us a report and says they see something abnormal and now we got to call you back and say, "Hey, we must have missed something and we need to now do a scan and maybe even go do biopsies in the operating room."

There is a couple of ways though that cytology can be abnormal. In most institutions, if it's positive for cancer cells or suspicious, then there really is cancer somewhere. We may not be able to always find it right away. Sometimes it can take six months, nine months before we can even find a cancer, but we know that we should be concerned. But oftentimes you might get atypical cytology and most of the time that means there's no cancer there and the cells just look a little irregular because you've had treatments in there like chemotherapy or BCG that makes cells look a little irregular, a little reactive. And so not every time that cytology is not normal doesn't mean there's cancer. And really the urologist will let you know if you should be concerned about it or not.

Dr. Yair Lotan:



Now, I could spend an hour talking to you about various tumor markers that are being developed or have been developed to help detect cancer early.

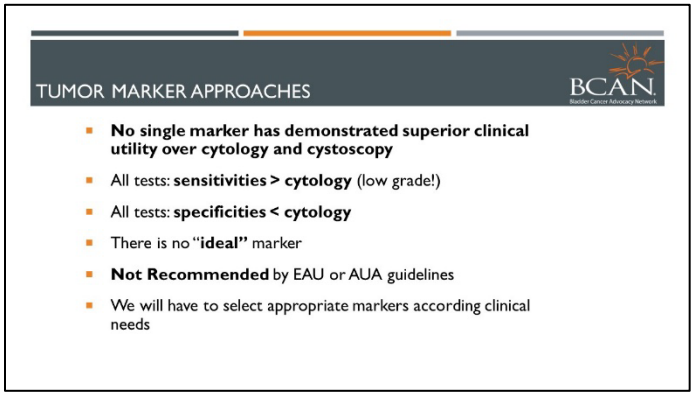
Basically, cancers are abnormal cells and what makes them abnormal is that they're growing faster than normal cells and they have mutations either in their DNA or their RNA or they're making a lot of proteins because they're trying to grow, proteins are the machinery of the cells. And so people have looked for any variety of these abnormalities, whether or not by looking for abnormal DNA RNA abnormal proteins, because the good news is that the bladder cancers are in the lining, which is right next to the urine. So you can look in the urine for some of these substances that you might not find in normal cells. The problem though is that sometimes if you don't see anything, and these markers are positive, you have the same problem with cytology is that you may not know where exactly the cancer is

PART 2

and maybe it's too small to even see with our cameras. And so we're stuck with what do we do next? Should we biopsy patients? And there's also a risk that there are some abnormal proteins because of the therapies we give so you can get false positive results.

So there's still a lot of studies being done to figure out how to best use these markers, but definitely there is a role, if you're already seeing something abnormal, if you see a red patch and the cytology is atypical, then the marker might help you decide should I have a biopsy or not?

Dr. Yair Lotan:



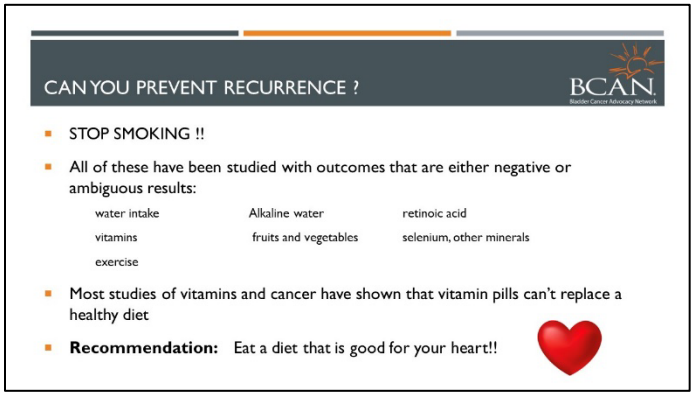
So the good news about them is that they're quite sensitive, even more sensitive than cytology, especially for low grade cancer. But specificity, which means, do you actually have cancer when they're abnormal, is lower than cytology. And so, as mentioned, it's really a matter of selecting appropriate markers for the clinical need and it's not something that we usually recommend to be done routinely.

Dr. Yair Lotan:

So let's talk a little bit about recurrence.

PART 2

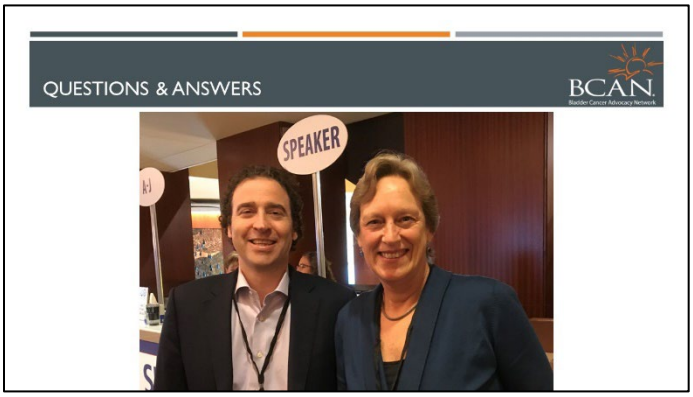
Dr. Yair Lotan:



How do we prevent it? Well, a lot of patients ask me, "What can I do?" And the easiest thing for me to do is stay away from smokers or don't smoke because there's a lot of evidence that smoking, which is the most common cause of bladder cancer will increase your risk for recurrence.

So it's not enough that it just causes it, but if you stop, you'll actually help reduce the risk for recurrence. It also helps prevent other bad diseases, lung cancer or heart attack, stroke. There's many things that tobacco is not good for, but if you don't smoke, then it's really much harder to do. A lot of patients want to take vitamins, they want to eat fruits and vegetables. I have patients that swear by it. Unfortunately, there isn't very good data to support doing any of these things. And what I tell patients is, "I don't really want you spending a lot of money on supplements and other things, at least not on my behalf, because there's no data." And we are data-driven people. I think that you can get a good... If you have good nutrition, eating fruits, vegetables, a heart-healthy diet. That's what you want to do. You want to exercise, but taking a lot of extra stuff hasn't been shown to help you.

Dr. Yair Lotan:



Well, good news for everyone. We made it to the end of our presentation and we're more than happy to answer any questions.