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WHAT'S NEW IN PREVENTION AND EARLY DIAGNOSIS OF ANAL CANCER IN HIV MEDICINE

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[video transcript]

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Welcome to Physicians' Research Network. I'm Jim Braun, the course director of the monthly meetings of PRN in New York City. Since our beginning in 1990, PRN has been committed to enhancing the skills of our members in the diagnosis, management, and prevention of HIV disease as well as its co-infections and complications.

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We hope this recording of Stephen Goldstone's presentation What's New in Prevention and Early Diagnosis of Anal Cancer in HIV Medicine will be helpful to you and your daily practice and invite you to join us in New York City for our live meetings in the future.

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PRN is a not for profit organization dedicated to peer support and education for physicians, nurse practitioners, and physician assistants and membership is open to all interested clinicians nationwide on our website PRN.org. And now, allow me to introduce Steve Goldstone, Assistant Clinical Professor of Surgery at the Icahn School of Medicine at Mount Sinai in New York City.

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Thank you, Jim. Thank you everyone for coming. I'm going to talk to you about some new stuff. Because I'm a surgeon, I'm completely egocentric and self-involved, so most of it's my research but I'm throwing in a little bit from some other people just for good measure, okay? Screening for anal cancer is very different than screening for high grade anal dysplasia. Can just see a show of hands. How many people here do high resolution anoscopy? Anybody? One, two. How many have it in their clinics or facilities or offices? So more. Okay, great.

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Anal cancer is often palpable or grossly visible and that's a bad thing because people don't complain about it until it's too bad because they're embarrassed and doctors no longer look for it or do rectal exams. Anal dysplasia is often non-palpable and not often seen without magnification staining. But before you start a screening program, you need to be able to deal with an abnormal result. Does your pathologist know how to read it? Can someone do high resolution anoscopy? Are there surgeons available, are there surgeons who are willing to talk to you about it? I just want to show you two cases quickly.

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This is one I've shown before. It was an anal tag. The guy was complaining about it because he said it got irritated when he tried to have sex. I told him forget about it and he still complained about it. After like six months of complaining, I basically just snipped it off at the base. I gave him a little lidocaine then

snipped it off at the base. And it was an invasive squamous cell carcinoma. So, I mean, it can look like nothing. Then this patient actually just saw about two weeks ago.

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He's a new patient with a chief complaint of condyloma for 18 months. He referred by his HIV doctor. 35-year-old HIV-positive male. CD4 277, viral load 327. His CD4 Nadir was zero. He complained of blood on the toilet paper for a couple of years. He said it's condyloma. It's getting worse. He'd been referred to a surgeon by the HIV doctor in 2015, not me, who told the patient was wiping too hard. His physical exam was significant for a right inguinal lymph node, which was rock hard and about 1.5 centimeters. And then I turned him over.

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And this is what he had. Now, this is a 35-year-old male. HIV-positive. And inside he had one small area of high grade dysplasia. Outside he had that giant cancer.

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He's a Stage IIIB. His cytology was LSIL and he had E6/E7 MRNA testing, which I'll explain to you in a minute, which was positive. PET CT showed that the inguinal lymph node was hot. He had some nodes on the other side but they were just reactive. And this is probably what's going to kill him. Not his HIV or anything else.

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The anus is different from the cervix. As a gay man, even I know that. The prevalence of HPV infection in the anus differs very much from the cervix. There's data pointing to higher HPV in the anal canal of women who are HIV-infected and even in women who are uninfected. The WIHS study showed consistently higher anal HPV rates than cervical and stratified across CD4 counts. And the prevalence of anal HPV infection varies greatly depending on the patient. Heterosexual men, it's about 12 percent intra-anal and about 7 percent are oncogenic. If you look at the perianal skin and intra-anal canal of heterosexual men, it's about 25 percent. And that's all because of auto infection, generally. They spread it with their fingers, touch their penis, wipe their ass, boom. HPV infection. And HIV-negative MSM, it's about 60 percent with about 20 to 30 percent having oncogenic HPV and HIV-positive MSM, they have oncogenic anal HPV infection until proven otherwise.

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Cytology is the screening tool that you've heard about. I'm going to show you some new stuff in a minute but it's pretty poor in the anal canal. It has generally decent sensitivity, not great specificity. You can see the top are four different series. Some are a mixture of HIV positive HIV negative. Some are just HIV positive. But what you see, if the sensitivity is high, the specificity is low and vice versa depending on the series. So, it's not a great tool. But when you look at a series on HPV cytology versus sensitivity and specificity, the key is this column here. HSIL cytology with a non-HSIL biopsy. In other words, if the pathologist tells them there's HSIL on cytology, does the clinician find it? And you see that Salit et al they only found HSIL 55 percent of the time. So, their screening sensitivity and specificity probably isn't that

accurate. Nahas didn't find it 62 percent of the time, so even worse. Lori Panther does a pretty good job. Too bad she left doing this and now works for industry. But she was pretty good up there in Boston at the BI and Fenway. She had a 25 percent. When I started, I was about 25 percent. Now fortunately, we're up to 95 percent. So if you have an HSIL cytology, they have HSIL pathology until proven otherwise, okay? And then you look here. Benign cytology with HSIL biopsy. In those series, varied anywhere from 5 percent to 12 percent.

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This is our 2010 screening results and it shows very few patients, only 2 percent, came in with an HSIL cytology. But what you see is of the benign cytologies, 20 percent had an HSIL biopsy and that's HIV positives HIV negatives. If we just look at the HIV positives, it was 38 percent. Cytology really, really sucks in HIV-positive patients as far as being a guarantee that there's no disease there. And if you see here our HSIL at the bottom, we were at 95 percent. ASC-H, we were about 69 percent. And so, cytology is at best a predictor of disease. I just want to show you the Sinai experience because my practice is a lot of HIV-positive gay men and now increasingly more women as they're self-referring themselves or gynecologists are referring them.

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At Mount Sinai we have a breadth of risk factors for HIV. If you look here, the MSM were the youngest group. The heterosexual men were the oldest. But what you see here is that the MSM had the highest rates of abnormal cytology, 62 percent. Heterosexual men, 28 percent. But once they had an abnormal cytology the risk of getting HSIL on biopsy was the same irrespective of risk factor. There was no statistical difference. And in this screening study, we had five cancers, four in MSM and one in a heterosexual male. So, I've been looking for a better screening tool and I think that one of the things we should do is start testing for HPV. Now, I'm telling you this but HPV testing is not FDA-approved in the anal canal. It's approved in the cervix but not in the anal canal. But most-- all labs will do it and almost every insurance company except Aetna will pay for it. So, what we did here, so you see here, our sensitivity for cytology, and this is 300 patients, was 77 percent. Our specificity was 52 percent. And this is ASCUS or higher. Our negative predictive value was 80 percent and our positive predictive value was only 50 percent. So, just because they have abnormal cytology doesn't mean they're going to have disease. But if we look at, looking at hybrid capture 2, hybrid capture 2 tests for 13 oncogenic types, 16 and 18 in men. 11 other intermediate risk types. So, if one or more is positive, you get a positive. And they use it a lot in GYN now for referring women with ASCUS cytology to colposcopy only if they have high-risk HPV. Hybrid capture was the first player in it. And you see what hybrid capture did was it raised our sensitivity to 91 percent. It dropped our specificity a little bit to 40 percent. Our positive predictive value was 46 percent but our negative predictive value was 89 percent. Hybrid capture had significant higher sensitivity and negative predictive value than cytology in HIV-positive patients, not in HIV-negative patients. Hybrid capture 2 plus cytology, we used them together, had higher sensitivity and negative predictive value than cytology alone. So, I felt that hybrid capture was a good initial screening test with cytology. So, then something else is out there now called MRNA, E6/E7 MRNA testing. Have you heard of it? Some of you may get it. So, what's MRNA? Well, I mean, I'm a surgeon so if I know it, I'm sure you all know it. MRNA is messenger RNA and E6/E7 are the two real oncogenic gene proteins

for-- one degrades Rb. And they're really important and we find when they're active, when the MRNA are active, we assume that the virus is active, that it's making bad viral proteins that will cause a lack of apoptosis and no longer repair of genetic abnormalities.

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And so, what they did was, so here they looked at the sensitivity looking at 16/18 RNA and they found the sensitivity was 62 percent, specificity raised to 81 percent, which was a little higher than just testing for 16/18 DNA. If they tested for five types of RNA, they raised the sensitivity to 81 percent and dropped the specificity a little lower to 65 percent.

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If we look at the DNA, you find a little lower specificity. When they checked for DNA for all 13 types, they found it to be the most sensitive but least specific. They are recommending that RNA for five types really has the greatest specificity over DNA. So, this is another potential test that some labs are running. And we're now looking at it in our office as well. We had a medical student last summer. He came up with some really good data which we're getting ready to submit. It's been presented. So, Cobas. Have you heard of that? Roche Cobas. Some of your labs are doing that. That will test for oncogenic HPV but also 16/18.

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And what we did was we compared the Cobas versus the hybrid capture and there was no difference in sensitivity/specificity in either test for the 13 oncogenic types. So, that was good. But if we just test for 16/18 and use that to triage, we find it drops our sensitivity way down to 47 percent versus 95 percent for oncogenic HPV in general, but it raises our specificity way up to 70 percent. If they test positive for 16/18, irrespective of the cytology, there is a very high chance they're going to have high grade dysplasia there. And the positive predictive value is 23 percent versus 34 percent when we look at 16/18 and the negative predictive value is high for both, 80 percent without 16/18, 98 percent without any high-risk type. What we did here, which is something very interesting, we looked at all our cytologies and looked at what the HPV positivity did, what the relative risk.

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If we use a benign cytology without high-risk HPV, gave that a relative risk of one, the highest relative risk is HSIL was 16 or 18 or HSIL that's HPV-positive and HSIL that's 16/18 negative, the risk is 221 times greater than a benign pap. But if you look here, all the way down here benign 16/18 positive, the relative risk is 31. So any time, no matter what the cytology is, the more you have 16/18 or the more you have high-risk HPV in there, the greater the odds are that you're going to find a high grade dysplasia. So, an LSIL cytology without high-risk HPV has a lower relative risk of having high grade dysplasia than a benign cytology with 16/18. Does that make sense? In my practice, we're using it so an ASCUS high-risk negative we don't get too worked up about. A benign high-risk positive or 16/18 positive we get worked up. So, that's what we're doing here.

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What's our screening exam? Someone comes in, they get visual inspection. Very important. Look, spread the cheeks and look, then use your finger around the outside to feel for lumps and bumps that might be hidden in the hair. Then an anal cytology or an anal pap smear. No lube. Has to be done before the lube. Then we do a swab for STDs, for gonorrhea and chlamydia, and we also do the throat and the urine too because many people are just doing a urine and it misses a third of the STDs. Then we do the digital exam. Then we do standard anoscopy. If they come in with puss dripping and an obvious STD, we still do the pap smear. Why? Because once you treat them, they may not come back. And you want to know if there's something in there to tell them to come back. So, we empirically treat someone with an STD, we test them with NAATs, but we also do an anal cytology then. We do not do an HRA then, even if they look like they have warts because all the inflammation inside the anal canal will really make it hard to appreciate disease.

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Who should we screen? There are no hard set guidelines. But in the international Anal Neoplasia Society, we're coming up with this. HIV-positive MSM with a good prognosis over 25. Our youngest anal cancer is in a 27-year-old. HIV-negative MSM over the age of 40 with no condyloma, no high previous history of condyloma or HPV-related disease. If they have HPV-related disease or history of it, we start them early. Younger MSM with HPV-related disease. Women with high grade cervical or vulvar lesions or cancer over 40. Probably all HIV-positive women over 30, HIV-positive men irrespective of their sexual orientation over 30. All men and women with perianal condyloma. All men and women with transplant-associated immunosuppression. We're seeing our worst dysplasia in transplant recipients, especially kidneys. Why? Because they tend to get one graft, it lasts 10-15 years, they reject it, then they get another one. So, they're immunosuppressed for long periods of time, much longer than the livers or the hearts, et cetera.

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HPV testing may even be more useful in non-MSM as a primary screening tool because those patients are less likely to have high-risk HPV. If you want to screen a lot of women or transplant patients, mainly just a swab for HPV is all we really need. And women who are transplant patients who have it then they should be referred for HRA. Large numbers of patients and it's lower cost than cytology and you don't need a doctor to look at it. So, you can batch them and do them in low resource countries. If you have someone who can really examine them. Might be more useful long-term. We're finding a lot of patients now who we've treated over the years no longer have high-risk HPV. So, that's good. Patient with chronic ASCUS and no dysplasia, post cancer treatment. It's a very difficult HRA. Do they still have high-risk HPV or not? Or chronic inadequate cytology. And maybe in the future in vaccinated populations.

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HPV testing. You still need to follow it. One negative does not mean it's always negative. We don't really-- we think that you probably never clear the HPV. You probably just suppress it. And the question is can they reactivate? HPV typing in a biopsy. Don't do it. Don't do it. If you get a wart and you send it for a biopsy, so what? I mean, it's going to have 6 and 11. You don't need to know that. If you biopsy

high grade dysplasia and they tell you it's high grade dysplasia, why do you need to know that it's got oncogenic HPV in it? You don't. The only time I use it is when I see these papillomas which don't really look like HPV and a lot of people have been treated for years with [?] or cryo and I biopsy it. And it comes back with some arucous [?] characteristics but not classic. I say type that for HPV. If there's no HPV in it, it's not a wart. It's just scarring, post-treatment hyperkeratosis and stop treating them. So, if you have patients you've been treating for a long time with warts, it's time to do a biopsy. You know, a little lidocaine, snip a piece off, send it to the lab, make sure it's really a wart and not just scar.

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Who do you start with if you're going to start screening? Those with HSIL or ASC-H cytology or cancer cytology are a must. But you run the risk of other cytology results having HSIL and cancer not being referred for HRA. Anyone with a palpable finding on a rectal exam needs a screening. Those who've been HIV-positive for decades and have had very low CD4 counts. You all know who they are. They have high risk of high grade. Those with prior history of high grade. Maybe they had a biopsy or a colonoscopy. And women with cervical, vulvar or vaginal cancers or high grade dysplasia are also at higher risk. I just want to show you a couple of older series before I get into newer stuff to show you what we're doing.

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This is my series that I've presented before of about 700 patients that we treated for high grade dysplasia.

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Our cure rate for a simple lesion was very high.

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It was 73 percent in a HIV-positive patient, 84 percent in a negative patient. The reason they recur is not because the lesion we treat comes back because they develop a lesion elsewhere.

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This is the Kaplan-Meier curve. The top is positive, the bottom is negative. And you see at one year, about half the patients have recurred. Again, not because of the lesion we treated, because they developed a lesion elsewhere. At two years, it's up to 68 percent in HIV-positives, 60 percent in HIV-negative. At four years, it's 80 percent in positives, 72 percent in negatives. And then it seems to plateau. Very high rates of recurrence, very high rates. So, I've been looking for something better, sort of like a leap. You know, where they remove the whole transformation zone in the cervix. We can't do that in the anus. And I'm going to get to this in a few minutes about this new treatment that I developed that the FDA has just approved. It's the only treatment approved for anal dysplasia, specifically for anal dysplasia. So, hold that thought for a minute.

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What's the risk factor for recurrence after treatment? HIV is the number one risk factor. The number of lesions that they have. High grade lesions is the second very high predictor of recurrence. Having had a low grade biopsy before is a predictor of not recurring. Not recurring. So, if patients have low grade, low grade, low grade and suddenly have a high grade biopsy, less chance of recurring. Why? Why less chance recurring? I don't know but I'm a surgeon so I'll give you my opinion and I'll give it to you with a lot of undocumented force. And I believe it's probably because they're infected with a less oncogenic type. Like not 16/18. Maybe 31 33 45. So, it's not as bad as 16 or 18.

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Five patients progressed to cancer. Only one of them was being actively treated for a cure at the time he progressed. Three of them had been lost to follow up and came back about three years later with cancers. And one we stopped treating because he was just too sick from HIV.

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So, this patient was treated over three years multiple times, multiple lesions. I biopsied him in the office and you can see high grade dysplasia there at the top.

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And a nice submucosa at the bottom, the pink. I took him to the OR and excised it. And what you see here, nice high grade dysplasia and cancer under normal submucosa. Hold that thought till the end. I didn't know what was going on. It was a tiny little lesion. We sectioned the whole thing looking for the high grade, for the point of invasion. Never found it. Where was this coming from?

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Here's our Kaplan-Meier curve out to 10 years. Two percent risk of progression. People who've done studies have had--

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One guy, 22 patients not treated, two progressed to cancer. Another, Bard Cossins [?] group, 40 patients not treated, 7.5 percent progressed to cancer. Watson at al., 55 patients not treated, 15 percent progressed. Tong at al. This is a prospective study from Australia and she looked at 574 patients. Four developed cancer within three years. Their progression rate was 1.2 percent per year. Not 10 percent a year. 1.2 percent a year. We estimate the lifetime risk of most people is probably 10 to 15 percent of developing a cancer, not 10 percent a year. So, with us in the treatment group, we had about a 2 percent out to 10 years.

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Perianal HSIL. I just want to show you this. 70 patients. I've never shown you this before. HIV-positives, 70 patients, HIV-negatives, only 11. And what we found-- so, this is what it looks like.

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Here there are two high grade lesions. Left lateral and right anterior. We ablated them in the office. And six months later, no recurrence. And then a year after that, he's got a recurrence left laterally. So we retreated it. We just looked at perianal stuff.

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First of all, all bit two HIV-positive patients had concurrent anal canal dysplasia, so they had disease within the anal canal. All but one HIV-negative patient had it within the anal canal. If you biopsy something in your office on the perianal skin and it comes back high grade, they have intraanal high grade dysplasia until proven otherwise. It doesn't exist by itself generally.

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Recurrence. Only one HIV-negative out of the 11 reccurred eight months following his first ablation. He was retreated and he's never reccurred out to now five years.

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The Kaplan-Meier curve in HIV-positives looks very similar to intra-anal but it doesn't peak quite as high.

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So, we compare anal canal versus anal margin, which is the top line, you see at one year we have 38 percent perianal recurrence versus 53 percent anal canal. At two years, it's 51 percent versus 68 percent. At three years, it's 59 percent versus 77 percent. So, it doesn't seem to recur to the degree perianally that it does intra-anally. And the time to recurrence is about half median time to recurrence for perianal lesions is a year. For anal canal, it's about six months. So, they're probably two different birds. What are the risk factors for a perianal skin or anal margin lesion recurring?

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Well, univariate analysis was each anal canal lesion was significant. Each anal margin lesion increased it, and it's CD4 nadirs self-reported of 100 to 200. When we look at multivariable analysis, the only thing that's significant is the number of anal canal lesions. The intra-anal disease is probably seeding the perianal skin and driving the disease.

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Now, some brand new data. This is not published. It's been presented a couple of times. This is, I think it's really great data but then, I'm the PI on the study. But Cornell was one of our great sites out at Tim Wilkin was one of the great sites on it. This was what we call our baby ANCHOR study. It was the prelude to ANCHOR where we randomize patients with little amounts of disease. They could have no more than 3 lesions.

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And they had to be less than 10 millimeters in Gradus [?] diameter. Then when we saw we were doing okay, we increased it to 15 millimeters. And we treated them with infrared coagulation, which is one of the first treatments I ever did. And so, they couldn't have had prior treatment with IRC. We randomized them one to one treatment or observation and we saw them every three months for a year with HRA. We only biopsied the treatment-- the observation group if it looked like they were getting worse. About 4 of them had biopsies during the first year but most didn't change. So, this was our baby ANCHOR. And at 12 months, we biopsied all lesions and if they were in the treatment arm, we would biopsy them and if they had a recurrence, we'd retreat them.

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We screened 176, enrolled 121. One withdrew immediately when he found out it was an observation. So, we really had 60-60 treatment versus observation. At one year, we had 54 who completed in the treatment arm. Of that, 52 were evaluable. Three withdrew. And anyone who was unevaluable or withdrew was considered a treatment failure, by the way, per protocol analysis. So, you need to understand that when I show you the results with a grain of salt. And at the one year mark, we had 57 return and were evaluable and then 3 withdrew from that arm. Baseline lesions. All the patients were-- both arms were exactly the same as far as most demographics except there were more Hispanic in the, for some reason, in the treatment arm.

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But people in the observation arm seen to have higher numbers of lesions at baseline than in the treatment arm. We don't know why. It's just randomization. So, in the IRC arm, 32 percent had more than one lesion versus 47 percent in the control arm. How did we do with treatment versus observation? So, a complete response.

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65 percent in the IRC arm, 28 percent in the control arm for a risk difference of 35 percent, highly significant. If we look at having some lesions go away, it's 75 percent in the IRC arm, 45 percent in that control arm, 30 percent risk difference. So, it was very significant. Treatment did a much better job of getting rid of high grade dysplasia than observation. So, lesions do regress. Here's a left lateral high grade.

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You can see it's kind of yellow on the far left. Here it is at three months. And then here is it at six months. At nine months it's really starting to turn black like the rest of the areas there. And at a year, there's really no sign of this lesion. So, this is a lesion that actually really did regress.

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How do we do treatment? How do we do? Well, this is very interesting. It shows you-- so, one of the sites had been doing this for a long time and the other sites had not.

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And you look here, you see that at my site, our complete response rate at a year was 80 percent in the treatment group versus 45 percent in the other five sites and our complete and partial response was close to 100 percent versus 55 percent in the other sites. Clearly, there is a learning curve here where there is a need to keep doing this over and over and you get better and better at it, I would hope.

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And so, baseline lesions, as I showed you before, two or three lesions increase the risk of recurrence 2.4 fold in the treatment group. Now I'm going to show you what has just been FDA approved. Medtronic paid for this research. Do you know about Barrett's esophagus Radio Frequency Ablation? Barrett's esophagus is columnar dysplasia. Not squamous but columnar. Growing up over squamous epithelium whereas in the anus, it's squamous dysplasia growing up over the columnar epithelium of the rectum. They used to targetly ablate Barrett's esophagus to kill it but recurrence was high.

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So, what they do is radio frequency ablation of the entire circumference of the esophageal transformation zone. And that drastically decreases recurrence. Drastically. With low risk of stricture, about 3-5 percent. It's a fairly delicate tool. So, I said, let's try it in the anal canal. First, we started doing it on individual lesions. Then we started doing it on a hemicircumferential basis, then a full circumference. So, this is the anal rectal wand, which we've developed just for this procedure. They refused to name it the Goldstone anal wand, which is what I wanted but they didn't do it.

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Hemicircumferential, we did on 21 patients. They were all HIV-negative. Circumferential, we did it on 10 patients and they were all HIV-positive but one. And you can see their demographics there. So, HSILs treated hemicircumferentially.

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We only treated half the circumference. If they had HSIL outside of half of the circumference, then they couldn't be in the study. They could only have it in one half of the circumference. So, we treated 35 lesions in 21 patients. Average, mean was one with a range of one to four. Quadrants with HSIL were one and the range was one to two. In the circumferential, we treated 29 lesions in 10 patients with a mean of two and a range of two to eight and most had two quadarants with a range of 1 to 4 for circumferential disease. The thing about this is the speed. The HRA took eight minutes versus 13 minutes on the circumferential. The treatment took four minutes for hemicircumferential and six and a half minutes for circumferential. Very fast. And this is what it looks like.

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You can see the lesion with the red arrow post treatment. There's very little change. You can see the black arrow showing a little of the S scar [?] sloughing. It's a little bit whiter down there. At 12 months, it's completely normal. And this is what it looks like after the circumferential burn. So, how did we do?

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Hemicircumferentially, and this is published by the way. At three months, four patients had a persistent lesion. Twenty percent. We retreated them locally and one patient recurred again at 12 months. Metachronous lesions in the area we treated, we had 3. One at 3 months, one at 6 months, one at 12 months. It's for 14 percent. But outside the treated area, we had seven or 33 percent. So, something was happening by doing a feel [?] treatment. We were decreasing the recurrence in the half we were treating. Does that make sense? I went on to do circumferential. And why did they persist? Why did they persist, those four lesions at three months? When I did the circumferential, which I'll show you in a second, we also added biopsies, post ablation biopsy of a single site in each patient. So, if they had four lesions, we only biopsied one. And I guessed where the lesion had been and I just took a biopsy.

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And what you see here is you see this S scar [?] sloughing away. It looks like normal high grade dysplasia but it's dead. Here you see the submucosa but you see a little focus of high grade there. Is that viable or is that going to slough? We don't know. But what I guess is this is why they recur quickly is because we're not going deep enough.

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If we look at our circumferential, you see we had three patients persist at three months. One patient we found the persistence at six months. Four, or 40 percent, persisted within a year. But after they were treated, no one developed another high grade again. So, it wasn't one and done. It was probably two and done, which is something we've never had with targeted ablation. And metachronous HSIL, a lesion where there hadn't been a lesion before, only one patient. The exact opposite of what we see in circumferential ablation. So, this is my new hot toy. All right.

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SPANC. This is coming from the boys down under in Australia. This is their quasi ANCHOR. By the way, I left ANCHOR cards outside. We can screen anybody for ANCHOR who is HIV-positive and over 35, never treated for dysplasia before, for high grade dysplasia, and can't have had HPV vaccine. We have a site. Cornell has a site. I left you cards out there. I left you our pretty bracelets which say the perfect butt and the phone number. And they're in the pastel shades of summer. So you can take them.

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They've enrolled about 300 patients, HIV-positive HIV-negative. This is their one year data. They combine the positives and the negatives. So, if you look at the top, they have 59 percent out of the initial 390 men, 59 percent had no high grade at baseline. At six months, 25 became HSIL positive. If you look at the HSIL positives down below, 115 became were still HSIL positive and 44 percent were HSIL negative. If you look at a year, what you see in the HSIL negatives was about a 16 percent progression to high grade dysplasia. If you look at the ones who are HSIL positive, it's about 21 percent cleared. 21 percent cleared. And if you look at our data from 076, which I didn't show you, we're at about a 22 percent regression rate also. So, we think there's probably a regression rate of anywhere to 20 to 25 percent. And it's probably a couple of factors. One, either the biopsy's removing the lesion or it's

stimulating an immune response, so the body's getting rid of it. Or it was never high grade to begin with. Or we're just not finding it. Like if you look there, 25 high grades at six months were positive. And only 10 at 12 months. Down here HSIL, 44 were negative at six months but at 12 months, another 10 of them became positive again. So, there is a lot of variability. Do we even find the lesions?

[00:46:32]

HSIL persistence versus clearance. They looked at the risk factors which we're now looking at. They found that in men with HSIL at baseline, 56 percent persisted for at least 12 months. 21 percent clearance at 12 months. Clearance of HSIL decreased with increasing age. So, older MSM had lower clearance. AIN2 was more likely to clear than AIN3. Persistent HSIL. If the HSIL was there at six months and it was there again in 12 months, it was strongly related to being HPV 16 positive at baseline and continuing to have HPV 16 detected. And larger lesions were more likely to persist over time. I want to show you two quick cases changing patterns of cancer.

[00:47:34]

This is a 56 year-old female diagnosed in 2000 and never had AIDS. She had a prior anal fistula. She came in with a lot of high grade dysplasia.

[00:47:50]

All over the place. And condyloma. We hyfrecatored her.

[00:47:56] She came in six months later and she had draining puss from a fistula on the outside. Her HIV doc had her on antibiotics. That's not going to work. We sent her-- she wanted to go to her local hospital.

[00:48:19]

She went back there. They drained her. It didn't get better. She had an MRI, which was read as an abscess.

[00:48:27]

You can see it posteriorly, the abscess with the dark white lines of the arrows. Those are the fistulas. She was taken to surgery again.

[00:48:40]

It was just a lot of acute and chronic inflammation. She didn't get better. They drained her a second time. And she came back to see me for a high grade dysplasia and she's getting worse a year later.

[00:48:55]

I called her surgeon at her local hospital, took her back to the operating room and recleaned out the fistula.

[00:49:03]

And now it's invasive squamous cell carcinoma. And here's a picture of it.

[00:49:12]

And then we get an MRI.

[00:49:14]

And this time, they say there is a cancer there on the MRI. But if you look, the picture looks exactly the same.

[00:49:25]

From one year apart. The difference is that it's grown in size from 4.7 to 5.4 centimeters, 3.4 to 5.8 and 1.5 to 3.2.

[00:49:39]

This is something for surgeons and people draining abscesses and fistulas and HIV-positive patients with high grade dysplasia. They may have a cancer in the cavity. So, that's our first one.

[00:49:54]

Now, my second one that I want to show you is an HIV-positive MSM with multiple high grades. Came back after treatment and he has a high grade in the left posterior up here at the top.

[00:50:14]

And when he wanted to go to sleep to get them all treated, when he was asleep, I could feel a lump higher up in his rectum under the mucosa.

[00:50:24]

So, I could really push the scope in far because he was asleep and I saw this very abnormal-looking rectal mucosa. You're well above the anus. You're up in the rectum here. And he's got this really abnormal rectal mucosa. So, I'm a surgeon. And when in doubt, we biopsy it.

[00:50:45]

So, I started cutting through it. And look what's under it. This really nasty looking stuff. And this is an anal cancer up in the rectum that was tracking from somewhere. And what you see here is--

[00:51:02]

I love this picture. Here's the cancer. Here's normal colonic [?] epithelium over it and here's normal squamous epithelium over it down in the anal canal. So, we never found a point of invasion and that harkens back to that first patient I showed you. We have five patients like this now who are presenting with cancers. One came in with a positive pet CT for the anal canal when he was having it after

treatment for lymphoma. And the only thing that lit up was the anus and we couldn't find anything. The MRI was negative. We followed him for a year and a cancer erupted through the anus.

[00:51:50]

So, something's going on. Conclusions. Anal cytology screening is an imperfect tool. HPV testing could improve specificity. It might be more useful as a screening test in non-MSM populations. Please don't forget a digital anal rectal exam. HSIL recurrence is largely related to new lesions. HSIL regression occurs. It's probably about 20 to 25 percent. And it's the treatment superior to eradicating disease. Wide field ablation might reduce recurrence. Beware of occult cancers with atypical presentations.

[00:52:34]

This is my ending slide. Okay, thank you.

[Video End]