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# DIAGNOSIS AND TREATMENT OF ANAL CANCER: HIGH CURE RATES, BUT AT WHAT COST?

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## **Diagnosis and Treatment of Anal Cancer: High Cure Rates, but at What Cost?**

**[video transcript]**

[00:00:01] Welcome to Physicians Research Network. I'm Jim Braun the course director of the monthly meetings of PR in a New York City. Since their 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 coinfections and complications. We hope this recording of Stephen Goldstone and Peter Kozuch's presentation 'Diagnosis and Treatment of Anal Cancer: High Cure Rates, but at What Cost?' 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. PRN is a not for profit organization dedicated to peer support and education for physicians, nurse practitioners, and physician assistants. Membership is open to all interested clinicians nationwide at our website PRN.org. And now allow me to introduce Steve Goldstone, Assistant Clinical Professor of Surgery and Peter Kozuch Associate Professor of Hematology Oncology from the Icahn School of Medicine at Mount Sinai in New York City.

[00:01:02] OK thank you Jim. We've got a problem. No one looks in the anal canal and if we do, we think of everything but cancer.

[00:01:13] So here's a patient and it's from 2011 that I saw. This is another doctor's notes where if you look here, he's coming in with chronic discomfort and itching. I mean you've all seen patients with anal itch. I would think it's probably almost as common as headache. And he'd been treated for cancer perianally. and this is a colon and rectal surgeon here in New York City, and exam deferred. No one did a rectal exam on this patient or looked. And he's going to treat them with calmoseptine ointment and do a fungal culture. Comes back a month later and he didn't tolerate imiquimod, I don't know where that came because he became febrile. Persistent severe circumferential dermatitis and then he said he started an antifungal cream on him. And then the end of the month he's complying with antifungal therapy, but he's getting worse. Persistent left posterior warty lesion. He's awaiting fungal cultures.

[00:02:28] So finally, two months later the fungal culture comes back, and it's negative. So the patient was very upset and he came to see me. This is not fungal dermatitis. This skin is red, white superficial ulceration. And then up here, this is not a wart. It doesn't look like a wart. It's ulcerated, it's nodular, it's thick and indurated. And then there's this area which is very ulcerated, very thick and white. Here's this warty thing there, and this is a cancer. No one had biopsied it. They had treated him for fungus and waited two and a half months. So be very careful when you call something a wart. It should not be indurated, it should not be ulcerated, it should not be red.

[00:03:36] So this is a great paper that's about to come out. I actually had the privilege of reviewing it and then writing an editorial on it. And it's coming out in December. And the group at Mass General looked at the SEER database between 1973 and 2014 for patients with AIN3, high grade dysplasia or squamous cell carcinoma in situ. And they identified 2000 patients, and if they had cancer before the AIN3 they took them out. So they were left with 2074 patients. During the follow up, 8.2 percent progressed to invasive cancer. Over a median followup of four years, estimated progression to cancer was almost 10 percent at five years. Only one third of patients who progressed were diagnosed with T1, the smallest cancer. So not only are we missing them, we're also waiting till they come in with a sizable lesion before the diagnosis is made.

[00:04:49] So what were the predictors of progression the age? 41 to 50 years old had the highest odds ratio of progression, 1.7 fold. Being male, 2.2 fold. And this is probably a marker for being HIV positive or MSM because SEER doesn't capture that. But then if you look at the treatment, how they were treated for AIN3, it doesn't tell you the frequency of treatment or follow up, but it does list certain procedures. And those categorized as ablative therapy seem to be protective, odds ratio of 0.3 whereas those treated with excision were almost odds ratio of 2. So why excision worse and why ablation protective? Well ablative therapy, we think, is probably a marker for high resolution anoscopy and targeted ablation which is what we've been talking about here for years. And surgical excision is probably something where surgeons saw or felt a lesion, could see it, and took it out, but then left all the other high grade dysplasia there which was then able to progress down the line.

[00:06:11] And here's the Kaplan Meier curve. So five year progression rate in the ablation group was 2 percent. In the no surgery group, 8 percent. And in the excision group, 12.2 percent. So why was the no treatment group even better? And these are all significant differences. Why was the no treatment group better? Probably, again it's conjecture but I'm a surgeon so I believe my own bullshit, anyway it's probably because it was an incidental finding. Like we take off hemorrhoids or we remove little skin things and send them to pathology and it comes back with focus of high grade dysplasia. So these are probably people who may have had more limited disease, but again we don't know.

[00:07:04] So this is a series of anal cancer which we never got around to publish, but we presented it. And so at the time of 2012 when we did it, we had 69 cases of cancer. 62 males, 92 percent HIV positive. Only 7 females, 14 percent positive. Mean age of diagnosis, again here we had 50 for the HIV positive and older for the HIV negative. So of the 38 screened before cancer, who developed cancer, almost 100 percent had antecedent high grade dysplasia that may have been treated or was never treated. So we found records of high grade dysplasia. Of 42 that we diagnosed with cancer, 50 percent the initial biopsy was only high grade dysplasia not cancer. So you need a high level of suspicion to go back. If the pathology board is suspicious of cancer can't rule it out. It's not enough to treat it. You need to excise it. If you can do it, send it to a surgeon or do much bigger biopsies. Of 51 patients that we had detailed histology on, 33 percent had superficially invasive squamous cell cancer. So minimal invasion.

[00:08:37] So here's an example I just want to show you. It looks like a cancer. It smells like a cancer perianally. And here's the initial biopsy where it's got this endophytic growth pattern, see how it's like trying to push down from the basement membrane. This is something that worries the pathologist. I'm worried grossly on the morphology, the pathologist here was worried on the histology. And then we went and did bigger biopsies, deeper biopsies. And what you see here are these little tiny islands breaking off. So this is what we call superficially invasive squamous cell carcinoma, less than a 3 millimeter depth of invasion. So this is the earliest kind of cancer that we've shown.

[00:09:26] So when we followed our patients with cancer for median followup of two years more than half, 56 percent, developed recurrent high grade dysplasia after a mean of less than a year. So this is after chemo radiation or surgical excision. Local excision had more recurring high grade dysplasia than chemo radiation, 89 percent versus 41 percent. So even with chemo radiation, 40 percent recurred with high grade dysplasia. This is not anal cancer from the 70s, where it was a little old woman follow them for five years, afterwards they don't have another problem, goodbye. These patients, especially the HIV positives, have persistent high risk HPV in their anal canal. They are at risk for cancers down the line and high grade dysplasia. 11 developed recurrent cancer. 7, or 10 percent, died. 2 from anal cancer. And of the superficially invasive 17 patients, we locally excized 13 and 1 developed recurrent cancer and had chemo radiation.

[00:10:45] So what this teaches us? When you go to examine a patient have a high suspicion for cancer. Dialogue with the pathologist if you do the biopsy. Re-biopsy it or better excise it, or send it to a surgeon who can excise it. Local excision might be adequate for superficially invasive cancer, but you need to treat the remaining high grade dysplasia. Follow patients for recurrent HSIL, I'd say ad infinitum now especially if they're HIV positive. We need to work to try to decrease lost to followup rates. Both San Francisco group and our group, we report high loss to follow up rates. And we really depend on the HIV docs, clinicians to really say 'hey you haven't been back in a few years, go get checked.' And anal cancer rarely arises de novo without any antecedent high grade dysplasia. So do a thorough exam.

[00:11:49] I'm just showing you this picture. So it's a nasty anus, it looks like a lot of high grade dysplasia. But look we spread it, spread the cheeks and you see this ulcerated lesion right at the anal verge. This is a cancer right at the verge. But wait, don't forget to look inside. Here's another cancer. So the digital anal rectal exam is critical. A really good exam in the office is critical.

[00:12:23] So post chemo radiation he came back to see me because of pain. We don't like to examine them right away. You can see he's all inflamed and swollen. This isn't recurrence. This is all necrotic in the inside, where the cancer was. We thought maybe he might have abscessed or something, so we examined him under anesthesia. It's nothing. I mean it doesn't look like nothing, but it's post radiation

change. So then one year post treatment he's doing a recurrence of high grade dysplasia here. So what happens? Sometimes they stricture down and you can't do an exam, you can't get your finger in. Well you can get a swab in for cytology but if you can't do an adequate examination, we need to examine them under anesthesia. You cannot just say 'oh it's post radiation scarring,' it could be a cancer coming back. And here we have inside, this is not a cancer it's just a recurrent high grade.

[00:13:34] And then here's another patient two years post chemo radiation and you can see these petechiae, these are all typical post radiation changes. We spread the anoderm and you see he's got recurrent warts, not high grade dysplasia. So it's critical that you do a good digital anal rectal exam.

[00:13:57] Don't examine a patient too soon post chemo radiation, we generally wait at least three months before we do an exam. You can biopsy areas of suspected dysplasia. They will heal and you can treat recurrent HSIL or condyloma, but don't be overly aggressive.

[00:14:20] So read the pathology report, because the surgeon may not. So this tells you at least squamous cell carcinoma in situ arising in AIN3. And then here what we see is one fragment shows marked atypia with dyskaryotic cells, paradoxical squamous maturation consistent with squamous cell carcinoma in situ. No definitive cancer is seen but given the tangential sectioning. So this pathologist is all but hitting you over the head that this is a potential cancer. The surgeon didn't see it and they went and burned everything up. So the problem with biopsying and treating, or like if you treat a wart that you think is a wart but you're not really sure without biopsying it is that you can be treating a cancer and missing it. So I usually say if something looks atypical in your office, a little punch biopsy or something before you use a little cryotherapy or imiquimod or something on it.

[00:15:35] And this patient came to see me, this is how I got the records, six weeks after being surgically treated. And you can see he was angry because his warts came back so fast. Well this is not wart, it looks like wart in places but it's not wart, this is invasive cancer. So fortunately he recurred locally quickly rather than distant. So worrisome signs on your exam in your office. Induration not good. Ulceration not good. If it looks like it's invaginating, going deep, not good. Rapid growth, something doubles in size, not good. Repeated recurrence, if you keep treating something externally or if you know how to do HRA intra-anally and it keeps coming back, think that something bad is going on.

[00:16:32] And now, and I'm going to show you some pictures, we're now seeing a different presentation of anal cancer which to me is the most worrisome. We're seeing submucosal lesions without a mucosal cancer, so it's underneath. You put your finger in and you feel like a little marble or a pea under the surface and the surface looks okay. And I'm going to show you a couple of those now. So here's dysplasia in a pocket, you can see it coming right out. Here it is again. Little friable. We treated it

and then there's a nubbin of it down here that's come back. We retreated. There it is again at six months. And then after a year, it's just healing granulation tissue. So coming out of a pocket, scary. Fistula. Here's a patient came in with a fistula and you see here's the external opening, this is magnified, and it looks like something nasty in the fistula. When I pushed on the skin right in the middle here, this giant goober came out. And this is dysplasia within a fistula, this what he looked like intra-anally. So also we're now seeing cancers in fistulas. And here's what I call invagination. You see this high grade instead of being the nice flat high grade, it looks like it's a doughnut like it's going down in. And here it is with Lugol's iodine with surrounding high grade, but these abnormal vessels and this invagination is something that we're starting to see a lot of now and it's particularly worrisome.

[00:18:23] So here's a patient that was treated for warts for eight years, with cryotherapy, cautery, imiquimod, everything under the sun. And he came to see us and here on the outside he had a high grade, but inside he had this invagination, it was really indurated and hard. We biopsied it. It's cancer. He went for chemo radiation. So one year post therapy, this is actually the invagination but it's now full of stool, I cleaned it out and nothing was there. It's just scar. But two years and three years he began to have recurrent high grade here, here, outside, and here this was just scar again. Then in five years it started getting more aggressive here outside, nasty AIN3. Right here at the verge, AIN3. Inside was just LSIL. But then this very ulcerated area with these heaped up edges, it almost looked like thick wart but it wasn't. I took it out, it is AIN3. And then at six years, here we have these heaped edges and a cancer in the middle. And here's a classic cancer right at the opening with this internal ulceration and these heaped edges. So this is a cancer again six years later, he's treated with an abdominal perineal resection. He cannot have excision again. He has two cancers there and he can't redo chemo radiation, he's already had the maximum dose. But we bought him six years with his anus and progressive discomfort helped him. The thing you have to understand if you just have high grade dysplasia, if you just feel a stricture, they don't need a PET/CT scan. They don't need a referral to an oncologist. They don't need a colonoscopy. High grade dysplasia is not an indication for colonoscopy, there may be other indications but high grade dysplasia in itself is not an indication, it's an anal disease. It's not going to spread all the way up, except in rare cases. And we published on that. You don't need a PET/CT unless you know there's cancer there, for high grade dysplasia you don't need it and you don't need to refer to an oncologist. They need better biopsies or more excision, and then if they have cancer they can go to an oncologist.

[00:21:19] And so this is what I'm showing you. I felt a submucosal nodule. I looked inside up the rectum and this colonic mucosa looks inflamed but it was right over this nodule. So I started taking this off with a little biopsy forceps and got into this nasty, nasty lesion in the sub mucosal which is an invasive cancer. And this is what it looks like on biopsy. You can see normal colon over it and cancer underneath it. So he had high grade dysplasia but he had no cancer in the anal canal that we found. This is a patient who presented with a fistula, two of them pointing. And went to surgery by a different surgeon and they put in what we call setons, and the patient didn't get better for a year. The patient got an MRI which was read as abscess and fistula. After a year of not getting better, they took her back to the operating room

and really cleaned it out again and this time it was cancer. And I just want to show you the side by side MRIs. Here is the abscess in March 2016 and fistulas and then in March 2017 it essentially looks exactly the same. It's twice as large, but this time they're reading it is cancer.

[00:23:00] So just some general thoughts from my patients after chemo radiation. I generally do not recommend anal sex, toys, or fisting post radiation because they got a lot of sphincter destruction and they can often later in life with time develop incontinence. So I don't want anything that could potentially damage the sphincter. Some of them do have it, but I'm just telling you I don't recommend it. I call radiation the gift that keeps on giving. So they end up getting a vasculitis post radiation and they get progressive necrosis of the sphincter muscles, they can get it of the skin. So that's why I don't recommend it. You can ablate recurrent HSIL and condyloma post radiation, they do heal. If a cancer was excised and a recurrence develops, another excision is possible or chemo radiation. If a cancer was treated with full dose chemo radiation and they get a recurrence, they can't be irradiated.

[00:24:10] So my conclusions are you must have high suspicion for cancer or you will not make the diagnosis. Condyloma must be seen as a marker for potential high grade dysplasia. So in your populations of HIV positive patients, whether they're men or women, MSM or heterosexual, if they have condyloma they have high grade dysplasia until proven otherwise. High grade dysplasia and carcinoma in situ are not cancer and should not be treated as cancer. They don't get the cancer re-work up until we show whether or not there's cancer there. And they don't get chemo radiation for carcinoma in situ or high grade dysplasia. Treating HSIL appears to reduce progression to anal cancer. Initial biopsy of cancer is often high grade dysplasia, but you must re-biopsy deeper, excise it, if you have a suspicion. Worry about cancer complicating what you think is just simple anal rectal pathology in HIV positive patients who also have high grade dysplasia.

[00:25:31] Thanks Steve. And now we'll move on with Peter Kozuch.

[00:25:36] Good evening. It is really wonderful to be here. While it is gratifying as a medical oncologist to be able to treat a GI malignancy with curative intent with just chemotherapy and radiation, it is always a bittersweet experience. Because I really do hope that there will become a time where the preventive efforts, really through vaccination and also early detection of precancerous lesions proves to be effective and the increasing incidence of this disease decreases. So just as again a reminder here, we are talking about cancers. Squamous cell carcinoma is that the vast majority are driven by HPV, we can prove that because there is a P16 mutation in these tumors. Which whenever we have a squamous cell carcinoma of the anal canal or a squamous cell carcinoma that is happening in the keratinized skin of the anal margin, even if the epicenter is not coming from the anal canal, it's coming from the anal margin going into the anal canal we don't think a sphincter preserving surgery will be oncologically effective.

That is an appropriate referral to a medical oncologist who will then partner with a radiation oncologist to try to cure a patient non operatively at first.

[00:27:09] So these are tumors that originate above the dentate line, have drainage similar to rectal cancers so they may have perirectal lymph node drainage, perirectal lymphadenopathy. Tumors that are below the dentate line depicted here, those are the very very distal tumors where the epicenter is there. Those are the tumors that can spread to the inguinal area. Node positive disease is N1 disease, regardless of the area whether it's inguinal, mesorectal, internal or external iliac. It's all considered N1 disease and we treat accordingly. The chemotherapy regimens are the same, the radiation treatment is also largely identical for node positive versus node negative disease. The size of the tumor may affect the dose of radiation. Standard staging is a physical examination with careful attention to the inguinal lymph nodes and the supraclavicular fossa, because that can be an area that might be missed on CT scan and is an area where spread can occur. For women there should be very very careful inspection of the vulva, a gynecologic exam including a screen for cervical cancer. CT/PET for invasive cancer is appropriate, it will upstage a certain percentage of patients. In some studies as many as 28 percent of patients we find are node positive. Does this necessarily affect our treatment? No, because stage 1 through 3 disease is treated with chemo radiation therapy.

[00:28:59] Very very quickly, a tumor that is up to 2 centimetres node negative is a stage 1 tumor. 2 to 5 centimeters is a T2, stage 2 tumor. Once you get to have node positive disease or a T4 lesion, your stage 3. But regardless we treat with a combination of radiation therapy and mitomycin and either infusional 5 fluorouracil or capecitabine. This combination has been proven since the late 70s early 80s to be more effective than an upfront APR, although in fairness I think the type of APR that was done in the 70s is different than the type of APR that is done now, where there is sharp dissection along the pelvic sidewall, similar to a rectal cancer. But it would require a permanent colostomy if you have an APR. So the standard of care now is chemotherapy with radiation. And we can treat patients with HIV, with controlled HIV, just as effectively as we can treat patients who are not HIV infected. If patients have poorly controlled HIV, we may have to modify the dose of the mitomycin from 10 milligrams per square meter, maybe we'll start at 7 milligrams per square meter for the first dose. And if things are going well, by day 29 of therapy we will titrate up to the full dose.

[00:30:45] So if patients have a history of HIV related complications, that would also be a time when we might modify the dose of mitomycin. The chance of cure, we will go stage through stage, is quite high for the early stage patients but if this is a later stage disease, we can have cure rates that fall down to the 60 percent range. The standard of care again based on this collective data over the past several decades is very very well-established. It is radiation to a dose of 5400 to 5900 centigray. Just to give you a little context for what that means, we treat prostate cancer typically to a much higher dose, about 7000 centigray. Head and neck cancers where patients may have a lot of disfigurement following chemo radiation is often treated close to 7000 centigray. So 5900 centigray for a bulkier tumor is long term



pretty well tolerated. As Dr. Goldstone was saying, there can be some post radiation fibrosis. Yes I think that the survivorship recommendations in terms of sex is certainly very prudent. I think most patients probably would yield to that, it probably it doesn't have to be told to them. Their mucosa may be easily ruptured, even with a rectal exam, you have to be careful for life quite possibly. But they do have very very good sphincter control. The issue of stool seepage, incontinence of either bowel or bladder is very very rare, for the most part patients have excellent bowel and bladder control. And even to agree sexual potency, although fertility issues need to be discussed if men or women are of childbearing age and want to either bank sperm or a woman wants to preserve fertility.

[00:33:06] Parenthetically I should note that T1 disease, a tiny tumor that might be a small focus of invasion I think is reasonably treated with excision, although it is not standard of care. The standard of care still is chemo radiation even if we think a tumor was fully excised. But I think everything is context dependent and if you are with a team of experts in high resolution anoscopy who can meticulously follow these patients, coupled with a medical oncologist, or again I think somebody who's very experienced in the treatment of anal cancer. I think imaging is certainly also reasonable because we can see a regional node or recurrence absent a local recurrence and we'll talk about that. So there can be inguinal recurrences without a local recurrence. There can be very perirectal nodal recurrences or progression in a patient who either got chemo radiation or had an excision for an early stage tumor. So I think in addition to high resolution anoscopy for somebody who gets excision, imaging CT scan of the abdomen, pelvis and also possibly an MRI of the pelvis at least every six months for the first two to three years after a local excision should take place. And hopefully that's easier to remember because that sort of survivorship surveillance imaging is what we would also do for patients who are treated non-operatively.

[00:34:39] So you see here that even if we do develop cancer, which the goal is to cut me and my colleagues in oncology out of business with regard to anal cancer. If you have an early stage tumor we have about a 85 percent chance of cure. But once you start to get a bulkier tumor, 5 centimeters or higher, we see that the local regional relapse rate starts to approach 50 percent. If it's a more invasive tumor the local regional relapse rate gets to 60 percent and then the patients have to go back to Dr. Goldstone or colleagues for an abdominal perineal resection. Again there's a chance of cure after that, approaching 50 percent, but I think patients ideally would like to just have about five and a half weeks of chemo radiation.

[00:35:34] So radiation considerations. Again we typically go to the 5400 centigray. Bulkier tumors we will go to 5900 centigray. Therapy is very very surprisingly well tolerated for the first three to four weeks of therapy. It is towards the end of therapy that patients may start to develop a fair amount of proctitis and we will support them through this with topical anaesthetics, sitz baths, stool softeners and supportive counseling. Chemotherapy related side effects, I think chemotherapy is a dreaded, a very dreaded issue. All chemotherapies can cause a varying degree of fatigue, nausea, and vomiting and

myelosuppression. The chemotherapy that we give for anal cancer is not particularly emetogenic, when you combine it with radiation it can be, but our anti-nausea regimens now are so effective that actual chemotherapy induced vomiting for anal cancer is anecdotal. I cannot recall a single patient who has had it. We are now worried about things like chemotherapy associated anorexia. Just parenthetically patients may say that the chemotherapy or the radiation is giving them a headache. It is extraordinarily rare for anal cancer or any GI malignancy to spread to the brain. What the overwhelming majority of headaches are due to is because of our anti-nausea therapy the 5-HT3 antagonists can cause headaches in about 20 percent of patients. For patients who we co-manage, I do think that we should be aware that the capecitabine, which we are largely using as opposed to infusional 5 fluorouracil, so the vast majority of your patients will no longer need a Porta Cath or central access. They will get two single doses, four to five weeks apart of mitomycin that can be given very safely by peripheral vein and the capecitabine, brand name is Xeloda, is again very well tolerated. But we have to worry about anecdotal cases of angina and if they are starting to complain of new shortness of breath and they're not anemic and they don't have a pulmonary embolism, we have to worry about a reversible cardiomyopathy that so-called Takotsubo cardiomyopathy. I will worry about that but because we will sometimes share call on these patients, it is something to concern ourselves about. I think mitomycin is a very feared drug. It is I think in general a very harmless drug for two doses. If you get to multiple lifetime doses which our patients do not do, there is a concern about hemolytic uremic syndrome, but with two doses where the lifetime exposure is no more than 20 milligrams per square metre we just don't see it.

[00:38:34] If a patient develops metastatic disease, a disease that is widely metastatic, more than one organ system we are trying to prolong their quality and quantity of life. Curing patients with widely disseminated disease unfortunately is not a possibility with chemotherapy. Cisplatin 5 FU or oxaliplatin and 5 FU are certainly very very reasonable choices. I think the latest regimen is a very well tolerated triplet of docetaxel cisplatin and 5 fluorouracil. And you can see here that the survival curves are quite good. Typically when a progression free survival is nine months you can figure that the overall survival will roughly double that, just because a patient progresses with metastatic disease they can still go on to get second and third line therapy and do fairly well or supportive care and do fairly well before ultimately succumbing to disease.

[00:39:41] I want to begin to wrap up by talking about immunotherapy nivolumab and pembrolizumab are PD-1 inhibitors. These drugs work in squamous cell carcinoma of the anal canal in about 20 percent of patients. When they work, they can work extraordinarily well and this is the class of drug that can cause widely metastatic disease. Chemotherapy cannot cure. I'm not saying that nivolumab and pembrolizumab, they're basically interchangeable drugs in terms of efficacy and side effect profile, we can get prolonged complete responses. I am treating a patient right now who's been on therapy for about 14 months and he did have brain metastases that were not completely controlled with whole brain radiation therapy and then went into a complete clinical response with ongoing nivolumab. So it can happen. Studies are underway combining pembrolizumab with a CTLA-4 inhibitor. And studies are

underway following chemo radiation therapy now with nivolumab as an adjunct to see if we can further improve survival outcomes.

[00:40:52] To be aware, typically during the first three months of PD-1 immunotherapy, patients are vulnerable to autoimmune issues. It can be a spectrum of autoinflammatory diseases. We continually monitor patients at each visit for thyroiditis which can lead to hypo or hyperthyroidism, colitis, pneumonitis it's not subtle when it happens, encephalitis can be subtle but we know to look for it, nephritis. Any -itis we're watching for it. Incidentally there's conflicting data, but these PD-1 inhibitors may actually decrease HIV reservoir. So that also may be an additional benefit. But patients with HIV can be treated with PD-1 inhibitors.

[00:41:38] Very quickly, if you have oligometastatic disease, just a single area of periaortic disease, liver only disease, after getting treated for local disease. We potentially can cure patients like this, we know we can do this with colorectal cancer we have nomograms, we have predictive indices for who we can cure. So multidisciplinary management of metastatic recurrence in highly selected patients with niche areas of metastases as opposed to wide dissemination can potentially be cured. There is such a thing as squamous cell carcinoma of the rectum, it is often an HPV driven disease as well. We treat it identically with chemo radiation and survivorship with C.T. scans on an ongoing basis.

[00:42:29] C.T. scans, patients certainly with anal cancer should have high resolution anoscopy, ongoing imaging at least for the first two to three years of diagnosis. And I think for the HIV infected patients monitoring CD4 counts on a very frequent basis, I know that after about two years your monitoring CD4 counts annually I think as a CDC guideline, that goes out the window. CD4 counts will fall in a significant percentage of patients, even though this is a more of a myelosuppressive as opposed to immunosuppressive regimen, in HIV positive patients CD4 counts will fall. And while I don't know for sure that they are a chemically induced fallen CD4 count is the same as a virally induced fallen CD4 count, these are the opportunistic infection incidents. I think following the CD4 guidelines for OI prophylaxis is reasonable but following them until recovery monthly, I think is very very appropriately cautious thing to do.

[00:43:34] And we certainly as the oncologists will continue to make sure to do survivorship including all supportive care issues, imaging, and we have to partner with the experts who are doing high resolution anoscopy. I think people like Dr. Goldstone who are so passionate about this, it's a huge relief to people like me. It's just an area that we need this and hopefully this is also being taught in either residency or medical school curriculum. Maybe we can discuss that as we have time for Q and A hopefully. Thanks.

[End]