“A Novel Immunotherapy Approach for 'Cold' Cancers” (Gary Onik, MD) [#86]

Brad Power
February 14, 2024

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Meeting Summary

Advanced cancer patients with solid tumors which don’t respond to immunotherapies (“cold” tumors), such as prostate, breast, and pancreatic cancer patients, look with envy at blood cancer patients with "hot" tumors, who can access immunotherapies and often get amazing results. In traditional immunotherapy the medications are given “systemically” (into a patient’s vein). The tumors of a patient with a solid tumor can see minimal amounts of the medication, and the patient’s normal tissues are exposed to the same levels of medications as the cancer. The result is that many solid tumors don’t respond to the treatment, and there is a significant risk that the patient’s normal tissues can be damaged.

Gary Onik, MD, a physician, researcher, medical device inventor, and a cancer patient and survivor, has developed several innovative techniques and instrumentation to treat cancer, including an ultrasound-guided cryosurgery (freezing) tumor ablation procedure for the prostate and for the liver. He has also developed a unique approach to immunotherapy that creates a cancer vaccine within the patient’s body. The “Onik Method” stimulates the immune system to do what it is supposed to do: recognize and eliminate the tumor. This approach enables immunotherapy for "cold" tumors such as prostate, breast, and pancreatic tumors, that usually do not respond to traditional immunotherapy. He successfully treated his own terminal prostate cancer using this invention.

What are the steps in this new internal cancer vaccine process?

1. Image the body (with PSMA, CT, or other techniques) to find a target tumor for the procedure.
2. Apply extreme cold with needle-like probes to freeze ("cryoablate") the target tumor, which damages the tumor, releasing proteins/antigens near the tumor.
3. Inject the tumor with immunologic medications that interact with the antigens from the dead tumors, which creates an internal vaccine, revving up the immune system to do its natural job of killing cancer cells. This vaccine circulates around the body and reaches other tumors to hopefully kill/shrink tumors elsewhere (the "abscopal effect").

Large volume tumors will sometimes need adjuvant traditional therapy, or systemic immunotherapy. Some patients will need other therapies later on.

What have been the results?

The results have been unique in the history of cancer therapy – it is the first treatment that so far has worked on every tumor type it has been tried on. In a published study, of 18 prostate cancer patients, 50% had a complete response. Patients with other cancers, such as pancreatic

cancer, also showed encouraging results. Of six patients with non-prostate cancer: 33% that had a partial response. The side effects were more limited than expected or seen with systemic immunotherapy. Responses have been durable; in Dr. Onik’s case, five years, and others have lasted many years.

How can you access this internal cancer vaccine?

This approach is currently available under “off label use” – the drugs and techniques are safe, but they are not being applied in the same way as when the drug or technique was approved.

A clinical trial has been approved by the FDA with a focus on pancreatic cancer. They are looking for funding now. Three centers have joined the program.

Until the trial is completed, a major limitation will be the cost to the patient.

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Meeting Notes

KEYWORDS

patients, tumor, immunotherapy, treatment, response, give, disease, adt, onic, cancer, talk, lesion, psa, liver, years, treated, working, bone, question, respond

SPEAKERS

Gary Onik (65%), Amit Gattani (13%), Allen Morris (9%), Gitte Pedersen (3%), Brad Power (3%), Ian Lewington (3%), Robert Gurmankin (2%), Paul Van Camp (2%), Brian McCloskey (2%)

OUTLINE

1. Cancer patient support and medical advice. (0:03)
2. Cancer treatment options with a focus on immunotherapy. (1:03)
3. Immunotherapy for hard-to-treat cancers. (4:51)
4. Cancer treatment outcomes and immunotherapy. (11:49)
5. Immunotherapy for cancer treatment with low side effects. (18:44)
6. Prostate cancer treatment options and genetic testing. (25:27)
7. Prostate cancer treatment with a focus on immunotherapy. (33:43)
8. Immunotherapy for cancer, including cold cryoablation and systemic immune cocktails. (42:42)
9. Immunotherapy customization for cancer treatment. (48:12)

SUMMARY

- **Cancer treatment options with a focus on immunotherapy.** 1:03
    - Amit Gattani is undergoing active treatment with Dr. Onik after reaching an impasse with standard of care treatments for his advanced prostate cancer, which has spread to his bone marrow and transformed to neuroendocrine disease.
    - He shares his experience with Dr. Onik's immunotherapy treatment for prostate cancer, discussing his initial research and decision to pursue the treatment.
- **Immunotherapy for hard-to-treat cancers.** 4:51
    - Gary Onik describes a new method of immunotherapy, the "Onik Method," which involves releasing tumor antigens using non-ablative freezing and injecting medications into the treated area.
    - He discusses using a combination of immunotherapies to treat cold tumors, including pancreatic, breast, and prostate cancer, which have shown no previous response to immunotherapy. [AM editorial: This is not true. Remember, Provenge the only FDA approved therapeutic cancer vaccine, period.]

    - A patient with metastatic pancreatic cancer experienced complete response to treatment.
- **Cancer treatment outcomes and immunotherapy.** 11:49
    - A patient with aggressive prostate cancer went from near death to 8 years cancer-free after treatment.
    - Researchers found complete or partial responses in 63% of prostate cancer patients, with fewer side effects than expected.
    - A patient with pleomorphic sarcoma and liver metastases had complete response to immunotherapy, but recurred two years later.
- **Immunotherapy for cancer treatment with low side effects.** 18:44
    - Unique treatment has worked on every tumor type tried, with low morbidity and durable responses.
    - Gary Onik discusses off-label use of FDA-approved drug for pancreatic cancer treatment, seeking funding for clinical trials.
    - Autoimmune side effects are limited, but myocarditis is a concern.
- **Prostate cancer treatment options and genetic testing.** 25:27
    - Gary Onik discusses genetic testing to predict cancer progression and potential treatments.
    - He discusses treatment options for advanced prostate cancer, including ADT.
    - He advises Ian Lewington to consider second-line therapy if PSA is rising despite Enzalutamide treatment.
- **Prostate cancer treatment with a focus on immunotherapy.** 33:43
    - Gary Onik discusses their formula for treating prostate cancer, including cryosurgical lysis, Leukine injection, and immune checkpoint inhibitors.
    - Leukine dose for subcutaneous injection is 500 micrograms per 1.9 sq m, but it's too expensive for widespread use.
    - Amit Gattani and Allen Morris discuss the use of ADT in prostate cancer treatment, with Amit suggesting it's not part of their protocol for auto vaccination.
    - Allen Morris explains that the exocrine pancreas may be immune privileged, potentially explaining why cancer recurrence occurs locally rather than elsewhere.
- **Immunotherapy for cancer, including cold cryoablation and systemic immune cocktails.** 42:42
    - Dr. Onik discusses the effectiveness of cold cryoablation versus heat-based approaches for solid tumors.
    - Dr. Paul Van Camp inquires about the use of a systemic immune cocktail after treatment to augment a more body-wide response.
- **Immunotherapy customization for cancer treatment.** 48:12
    - Brian McCloskey and Gary Onik discuss customizing immunotherapy cocktails with proteomics and other diagnostics to improve treatment outcomes.
    - Researchers are eager to collaborate and share data to improve cancer treatment outcomes.
    - The innate immune system plays a crucial role in cancer treatment, but its effectiveness is difficult to assess due to lack of understanding of its function in individual patients.

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TRANSCRIPT

Amit Gattani

I got treated by Dr. Gary Onik in the middle of January this year. I'm in active treatment with him now. You may know from various posts in the community that I had reached the end of the line on the standard of care treatments. They haven't been working for me for quite some time, but they kept giving me some extensions. But given my disease has spread in the bone marrow, my myelosuppression is very, very high, which means hemoglobin below 8 platelet counts. Generally my hemoglobin would hover between 6 and 7. With a little bit of blood transfusion, it'll go up. But what it meant is that I was not going to be accepted in any of the trials. The trials want hemoglobin about 8 typically.

Another complexity has been that my disease has also evolved into a neuroendocrine disease. With neuroendocrine disease, it's not pure adenocarcinoma. Trials generally don't accept mixed cancer types because they are trying to prove a particular point in a particular direction. The hemoglobin is a cutoff that I couldn't meet. So for the past four or five months, I've been searching for various alternative treatment options, and I came across Dr. Onik through a conversation that happened here in CPL originally. His name came up, and I started to look into that, and what this could mean to me. I had already gone through an immunotherapy trial, which didn't work with Keytruda.

As Dr. Onik will explain, this is an immunotherapy treatment. But it is a different approach to treatment. Then I started to ask, “Okay. Who else does this approach?” I explored that idea with a few of those that I could find that use this type of approach. I finally concluded that Dr. Onik is my best choice for treatment. I put my eggs in that basket, so to say. My treatment was five weeks back. We're still in the process of figuring out how effective it is. We'll know in a couple of weeks. Two things will happen: my PSMA scans will be back, and then my biopsy from NextGen in Germany will be back. That will give us a forward-looking direction.

I'll hand it over to Dr. Onik to introduce his specialty and the treatment that he is providing.

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Gary Onik 4:51
We're doing intratumoral immunotherapy. We feel that it is the next frontier in immuno-oncology versus giving the medication systemically, like they are doing right now.

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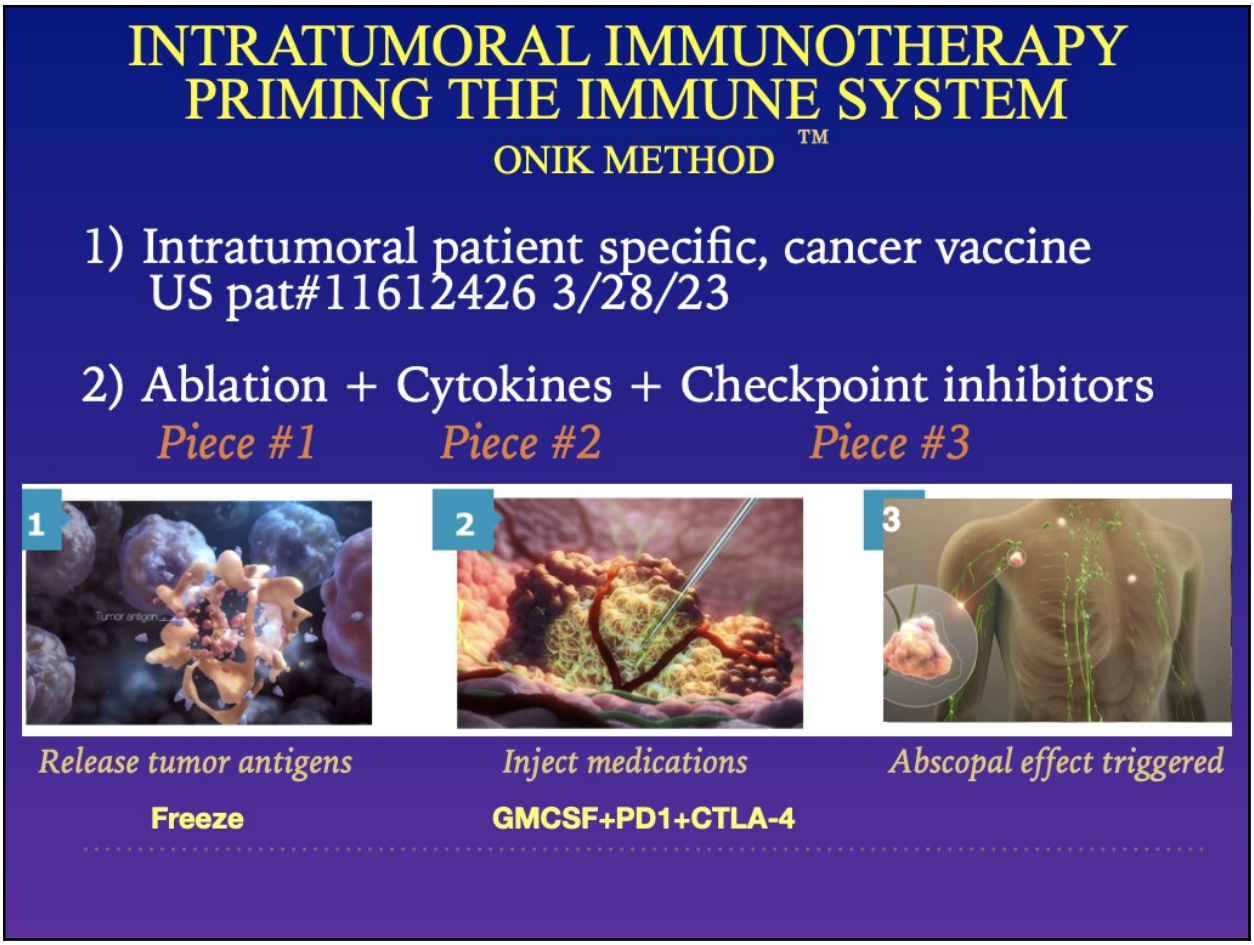
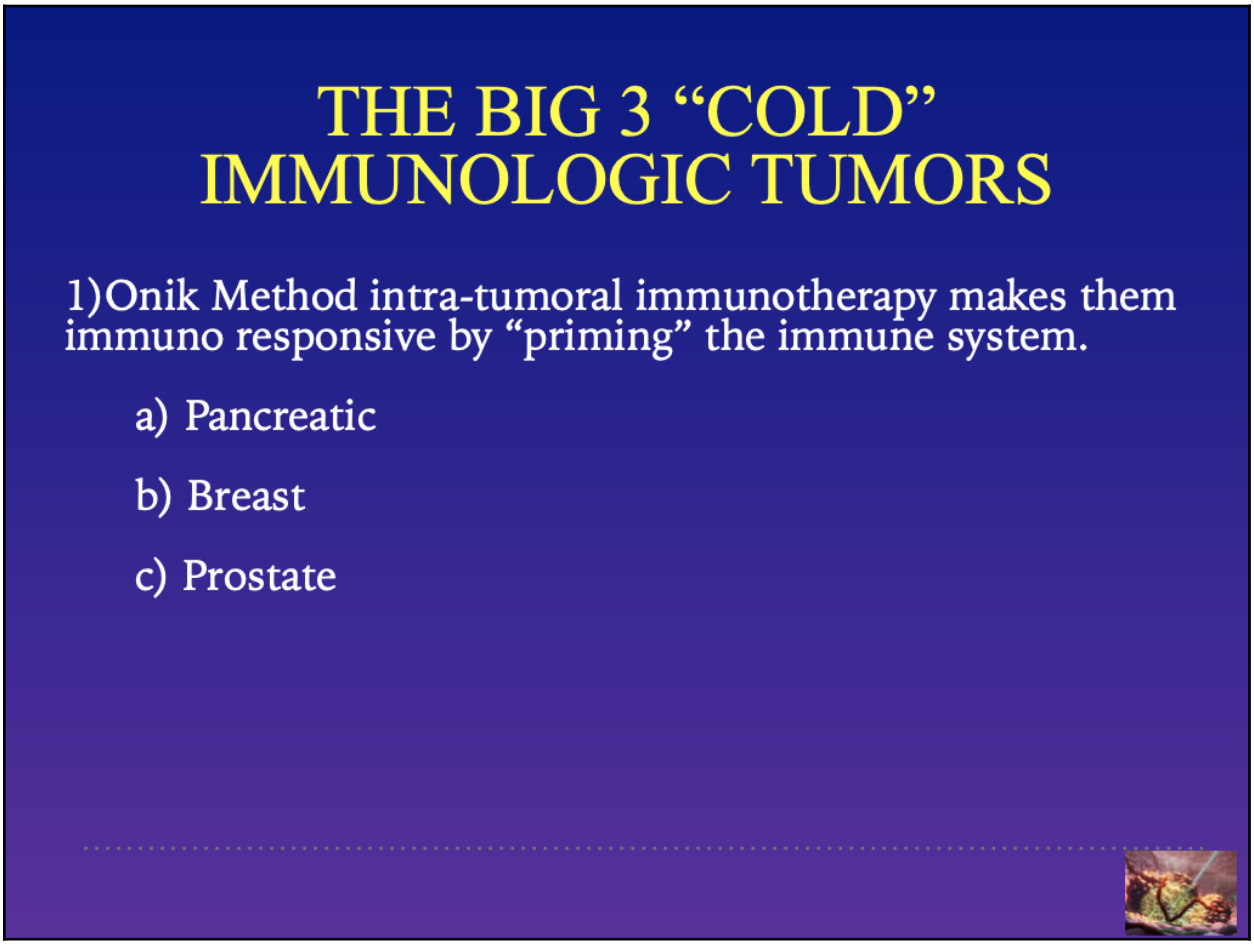


Let me show you what the process includes. For now, we're going to call this the “Onik Method”. It's got other names, but for this forum, let's call it the “Onik Method”. We're priming the immune system to react to the drugs that it didn't react to before and to unmask the tumor, so it can be recognized.

1. Piece number one is a release of the tumor antigens. We do that using something called a “non-ablative freeze”. By the way, all of this is covered in a patent that was just issued in March of 2023. I can present it to you without any worries. We use this very special type of freezing, and we release the tumor antigens without killing the vasculature and the mechanisms for immune cells to get into the lesion. If you do a regular freeze, it's an avascular lesion, and it doesn't do anything.
2. Piece #2: Once that thaws, and we have these released antigens, we inject medications into that area:
    a. GM-CSF (Granulocyte-macrophage colony-stimulating factor), also known as Leukine, also known as sargramostim (an immune system stimulator),
    b. a PD-1 inhibitor, (Programmed cell Death protein 1, a “checkpoint inhibitor,” prevents the “off” signal from being sent, allowing the immune system T-cells to kill the cancer cells),
    c. a CTLA-4 inhibitor (Cytotoxic T-lymphocyte associated protein 4, another checkpoint inhibitor)

   d. Sometimes we add in a PDL-1 (another checkpoint inhibitor). We can talk about why we might want to have both of them involved.
   e. Sometimes we'll use a LAG-3 inhibitor (Lymphocyte-Activation Gene 3, another immune checkpoint drug) if our genetic testing shows that that might be of any value. We stick all of these things together in one place.
3. Piece #3: That hopefully will trigger what is called an “abscopal effect” that will train the lymphocytes to go to other areas in the body and kill tumors that are throughout the body. We only treat one small lesion. Hopefully we'll get numerous lesions to react to that.



There are three tumor types that are called “cold tumors”, and these are three very important tumors: pancreatic cancer, breast cancer and prostate cancer. There are no approved immunotherapy regimens for these cancers. *[Editor’s note: Provenge has been approved as an immunotherapy for prostate cancer.]* They have tried all sorts of ways to get a positive reaction, including adding other chemotherapies to the immunotherapy. There are no responses for these three very important cancers.

What do we do with these cancers that have never been shown to react to immunotherapy?

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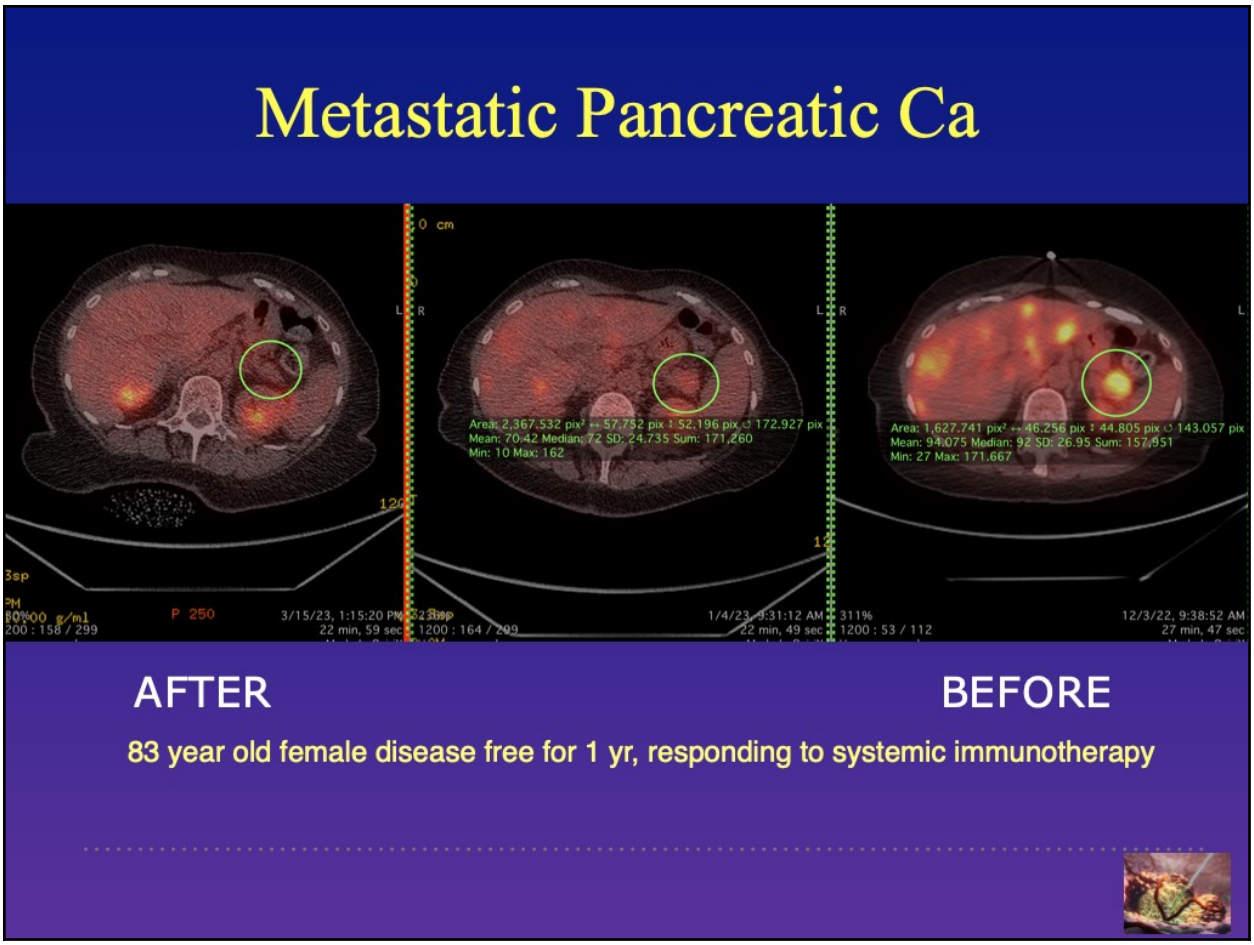

Here is a patient, an 83-year-old lady who had metastatic pancreatic cancer, adenocarcinoma of the pancreas. Because of her age and her medical condition, she really wasn't a candidate for other treatments and the FOLFIRINOX major chemotherapeutic agents. Here's her primary cancer in the tail of the pancreas. This is just one slice of her scan. She has numerous lesions within her liver. Her lifespan, literally, was measured in months, if not weeks, with this tumor burden in her liver. At one month, you can see that the activity in the PET scan has markedly decreased. The tumor looks like it's a little bit smaller, and the lesions in the liver have markedly decreased in their intensity. Here at three months you can see that the tumor is gone. These are kidneys, so don't worry about those, and there are no lesions left in her liver. In a tumor that doesn't respond to immunotherapy, this is a complete response. She had a recurrence in her pancreas at one year, and we are working on dealing with that. But her liver remains disease-free.

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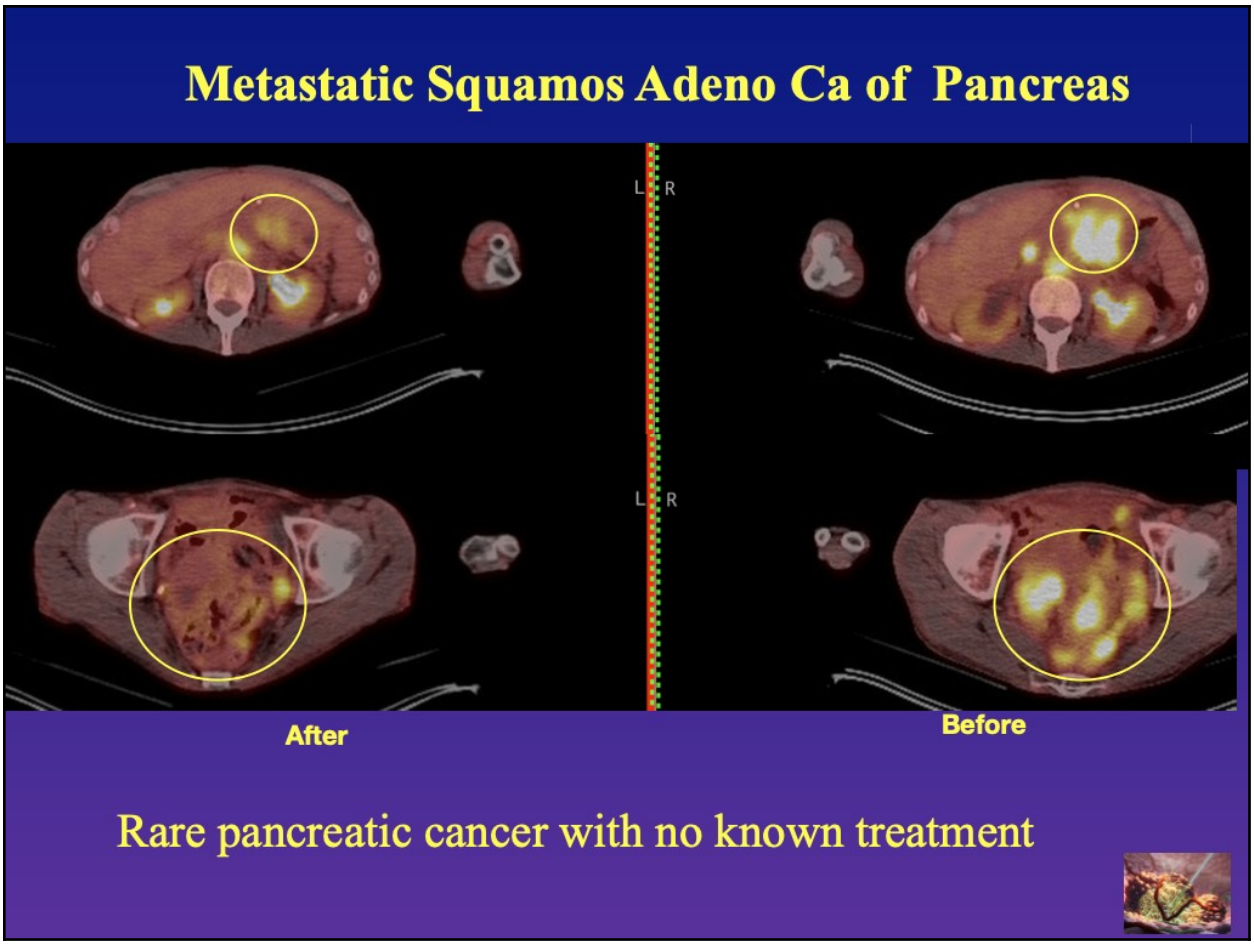

Here's a patient with a very rare cancer, metastatic squamous adenocarcinoma. Just a handful each year. No known treatment. You can see here is her primary. This is a disease that's throughout her peritoneum (abdominal lining), and you can see a marked response, and in the primary tumor.

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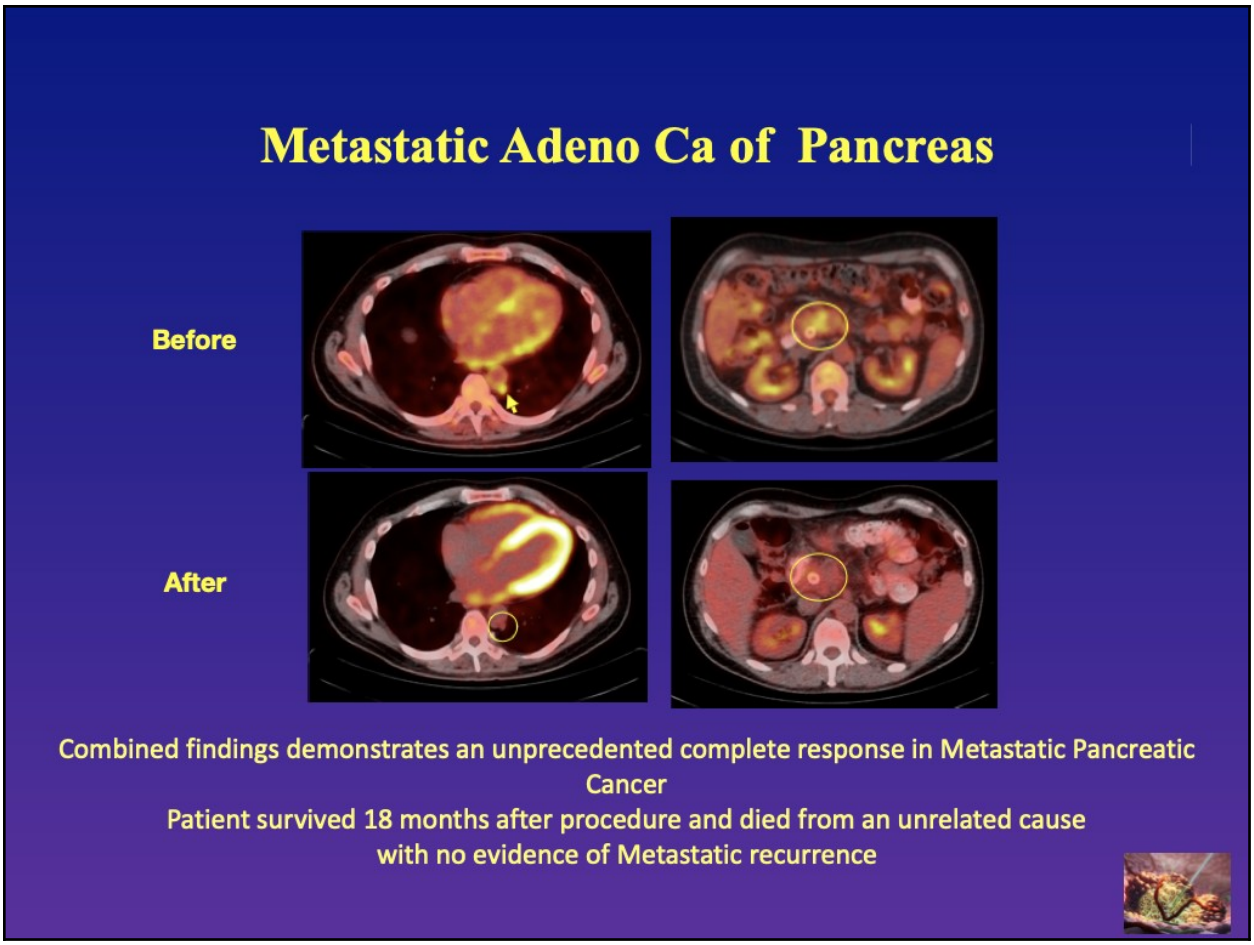

This is the first patient we did with a pancreatic cancer node in the chest, primary tumor here. The primary tumor has no activity, and the node in the chest has shrunk and has no activity. This was a complete response in the first patient we treated with pancreatic cancer.

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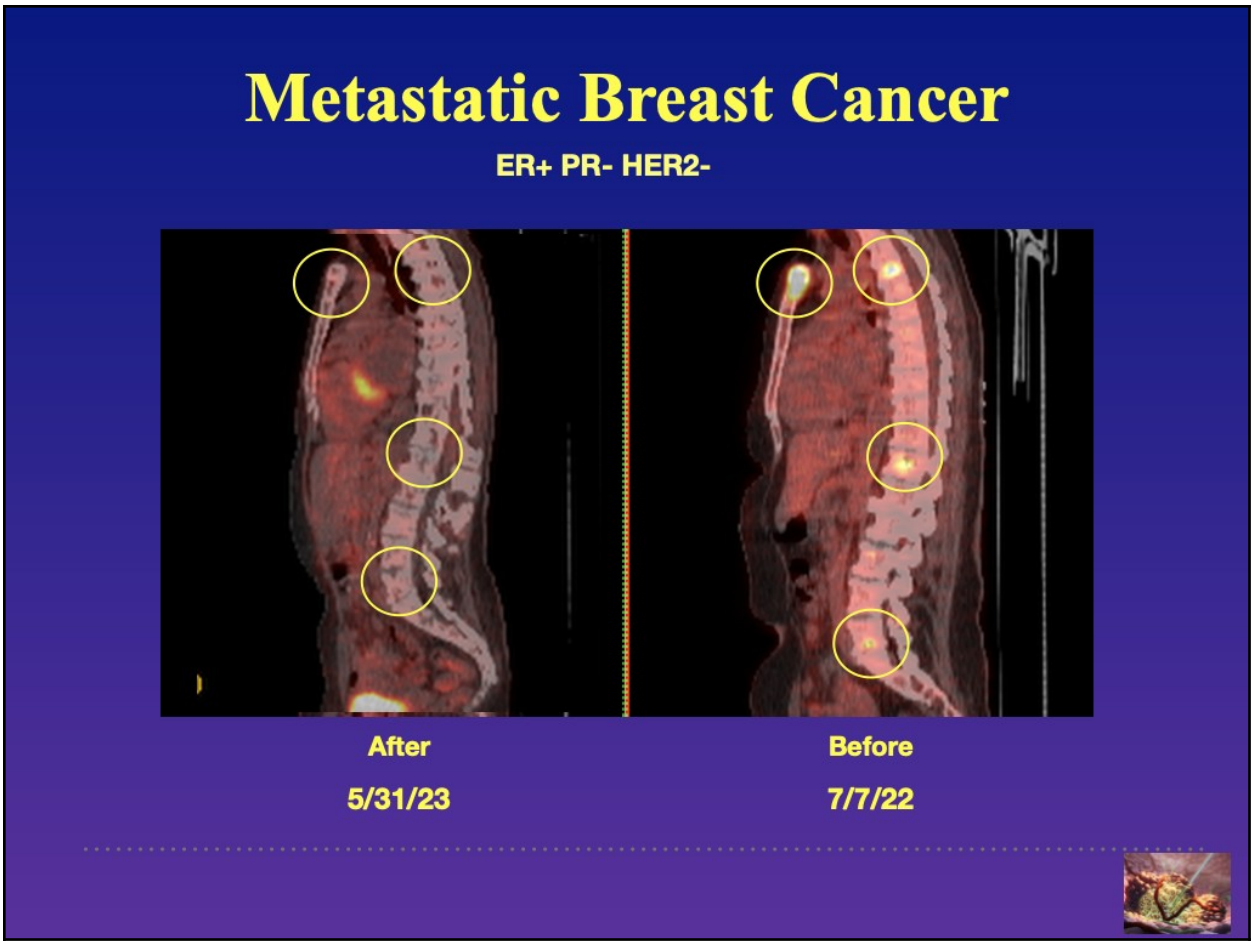

This is a patient with metastatic breast cancer. Numerous bone lesions throughout her spine, sternum, and many other areas. This is her heart. Don't worry about that. But she has gotten a complete metabolic response in this, and she's going on a full year with no evidence of disease.

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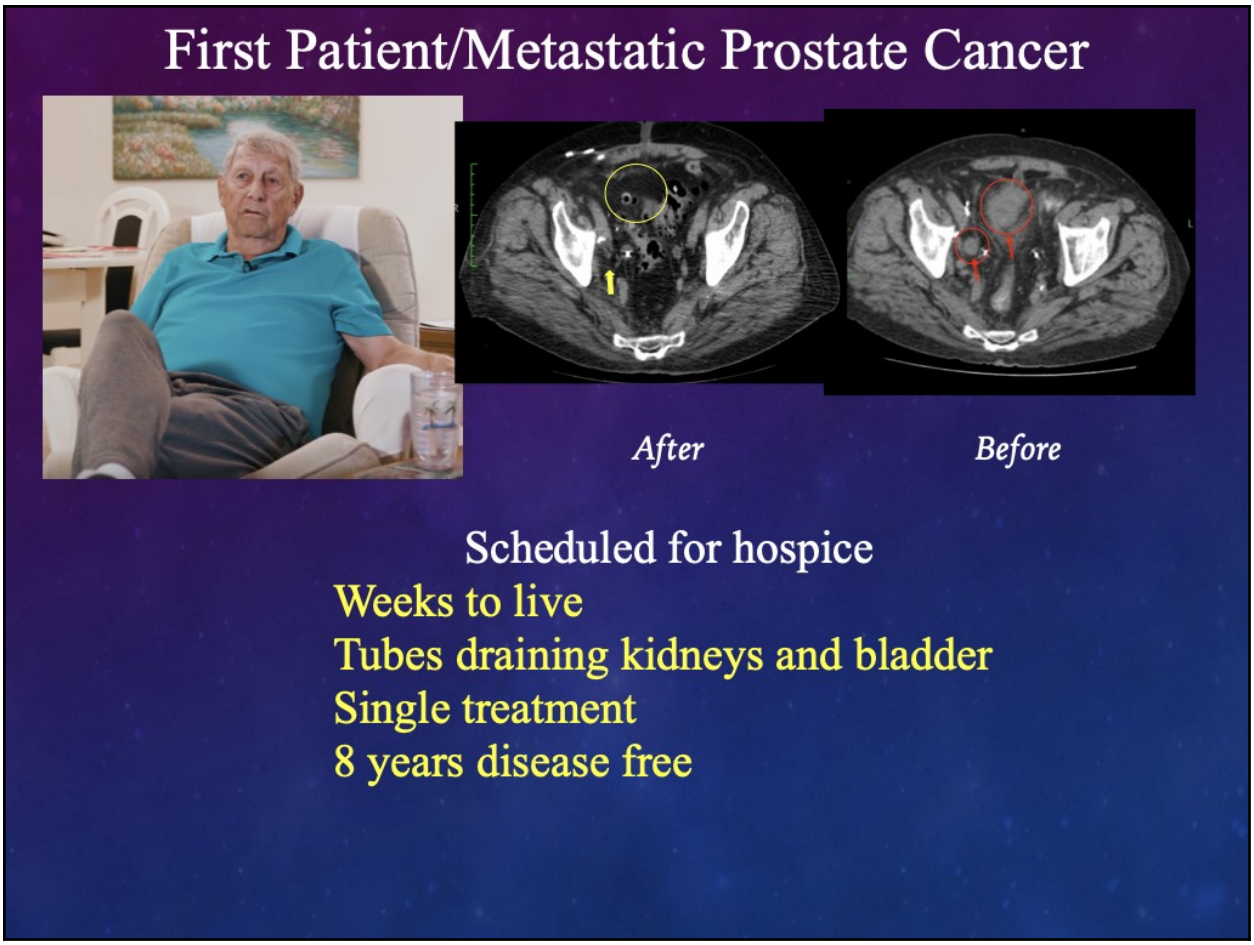

This patient with metastatic prostate cancer is the first patient we ever treated. You can see his scans. He's got a tumor growing out of the bladder, and he had multiple nodal disease. Seven weeks after the treatment, he had no evidence of the tumor, his PSA went to zero. He had had a radical prostatectomy, and a recurrence after that. He literally had weeks to live. He was going to hospice. He had one treatment, and he is now eight years going on nine years free of disease with a castrate resistant metastatic prostate cancer.

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This is my personal experience. I seem to look better in that picture than I do in person now. I don't know why. It's a couple of years ago, I guess. I was diagnosed with a very aggressive cancer. My PSA was 138. I had mets in my bone and pelvis and lymph nodes throughout my body. I underwent two treatments, two cycles. I just had my five-year survival party with no metastatic disease in the beginning of December.

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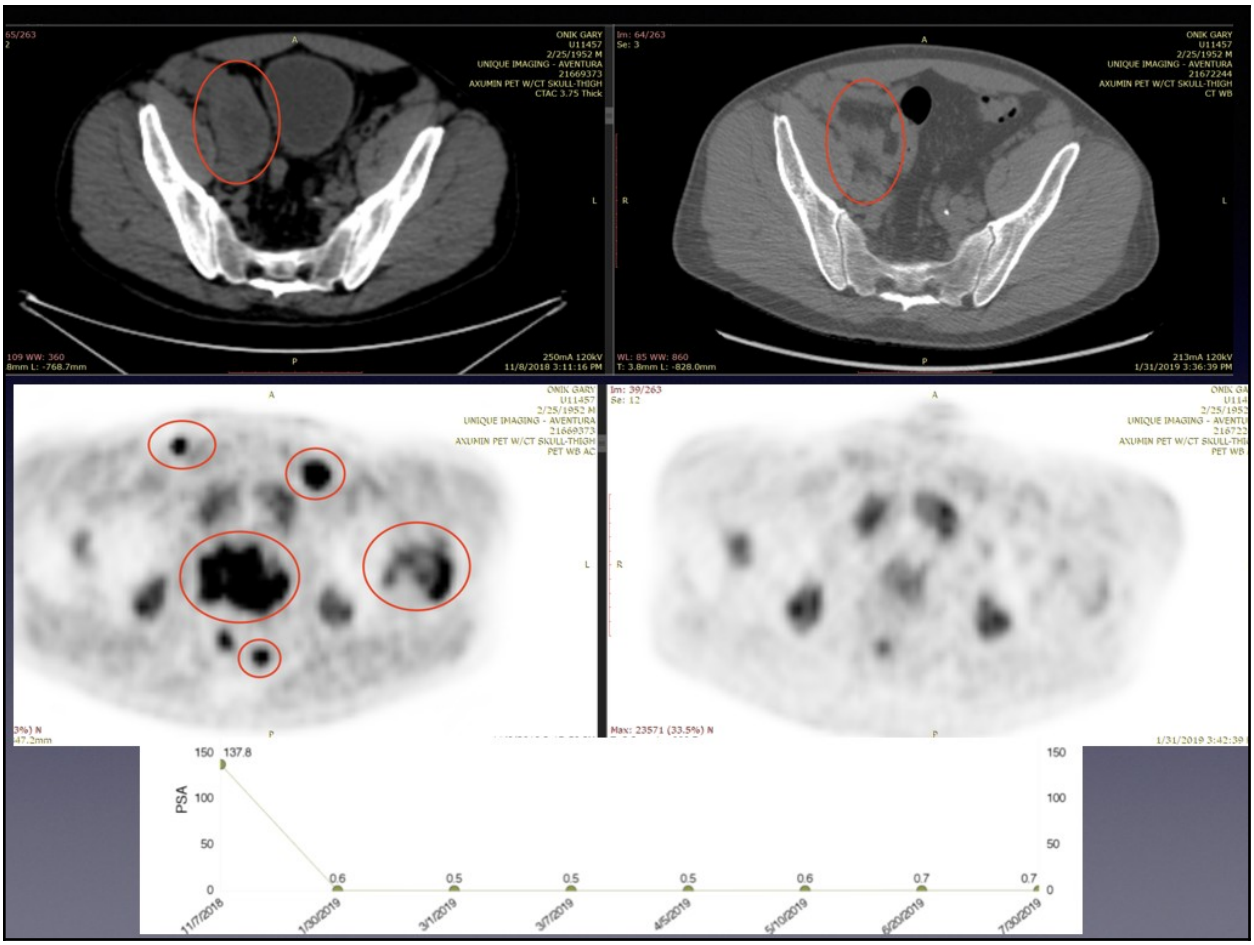

Here are some pictures: you can see the large pelvic mass. After the treatment that was gone. Here you can see the PET scan. You can see this is my prostate, a huge prostate tumor, multiple nodal masses, and a bone met. All of that resolved, and my PSA went down to 2.7. It's now about 2.4. I remain without evidence for metastatic disease.

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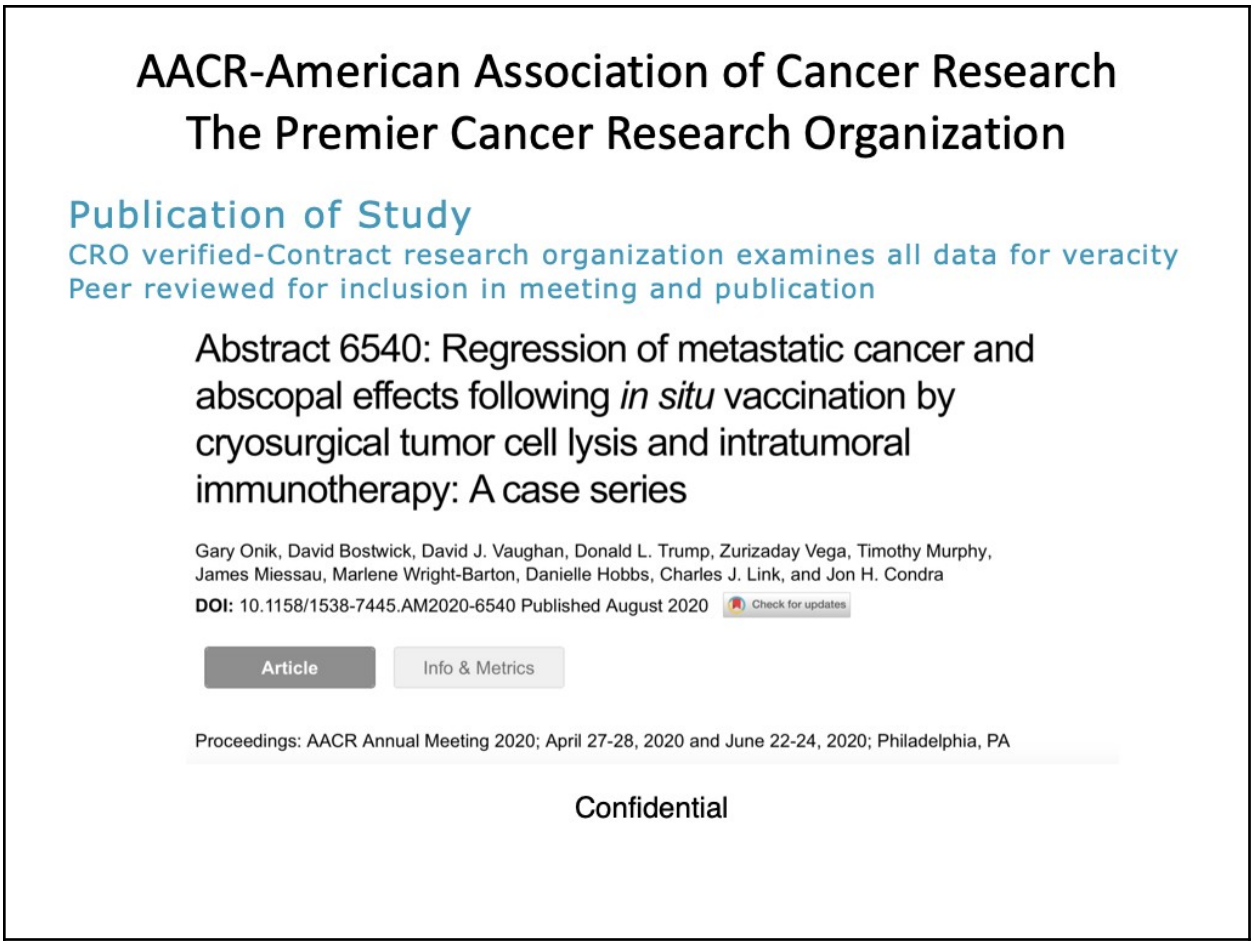

We took our first 27 consecutive patients, and we basically did a study. It was a retrospective study, but in a sense a prospective study, because results were followed prospectively. But we went back and looked at these patients. We had a contract research organization examine all the data as if it was a regular trial. This was peer-reviewed, and we sent it into the American Association of Cancer Research, which is the premier cancer research organization.

Gary Onik 14:44
These were our results. We had 18 evaluable prostate cancer patients, and 50% of those patients had a complete response. Six patients with non-prostate cancer: 33% that had a partial response. The side effects were fewer than expected.

We had one death related to a cardiac event. We've done about 100 patients since then. We have not had any mortality since that point. What was the cause of this? We think it was a pulmonary embolism. This patient was bedridden and already had ulcers. When we treated her, she had a marked response, and she started walking around. We were remiss in not giving her embolic prophylaxis.

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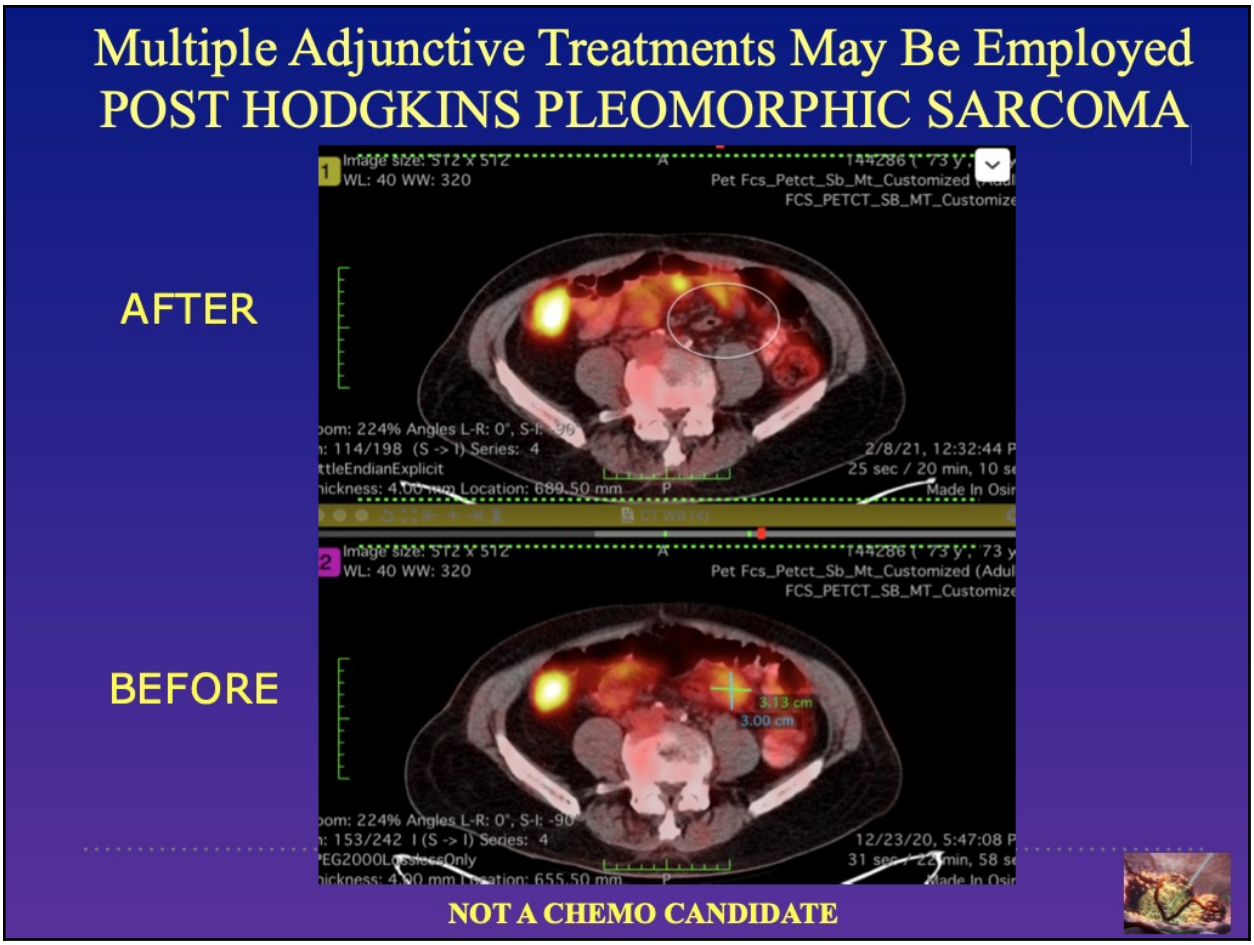

Gary Onik 15:58
This is a patient that was my college buddy. We used to kayak together. He had a pleomorphic sarcoma, to his mesentery, with multiple tumors, and liver lesions. He was not a chemo candidate because of his heart problems. We treated him. His intra abdominal tumors responded, and most of his liver tumors responded. I'm going to show you what that means.

This is a very specific treatment. It's specific to the tumor that we are making the vaccine attack. Not necessarily all tumors that a patient has, if they've got a large number of mets, have the same genetics. A patient might have disease that responds, and some disease that doesn't respond. A patient might have a large volume of disease, and they get an excellent response, but their immune system becomes exhausted. So they may need adjunctive IV medication. This is really, in a sense, the priming of the system. The first potential treatment in a series of treatments to get the patient to “no evidence of disease”.

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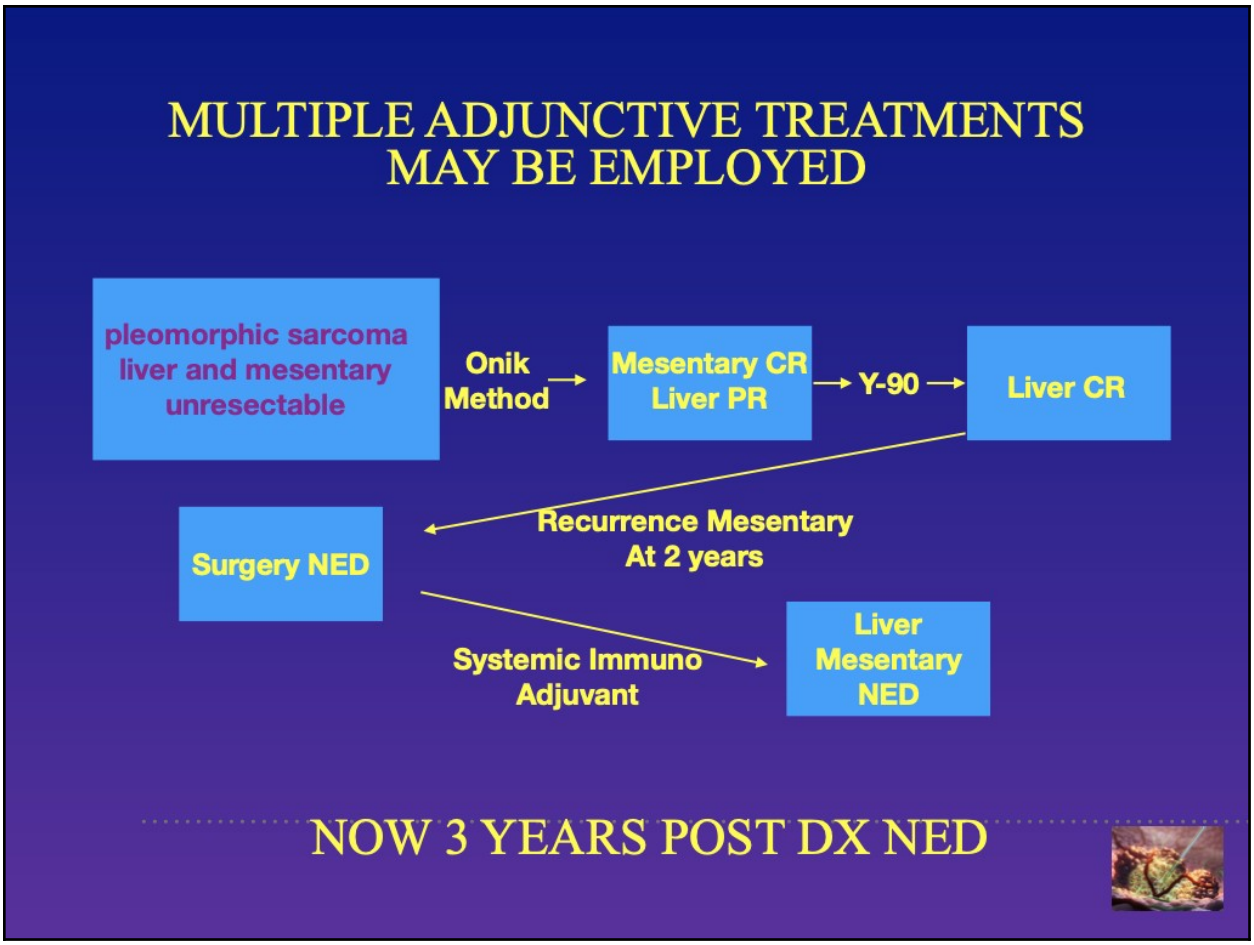

He had the pleomorphic sarcoma, liver mesentery. He was unresectable. We treated him. His mesentery had a complete response, and his liver had a partial response. He got Y-90, and his liver got a complete response. Then two years later, he had a recurrence in the mesentery. But it was surgically resectable. So he had surgery. He has no evidence of disease. We have put him on systemic immunotherapy as an adjuvant to prevent any disease from growing up. At this point, there remains no evidence of disease in terms of the liver and the mesentery.

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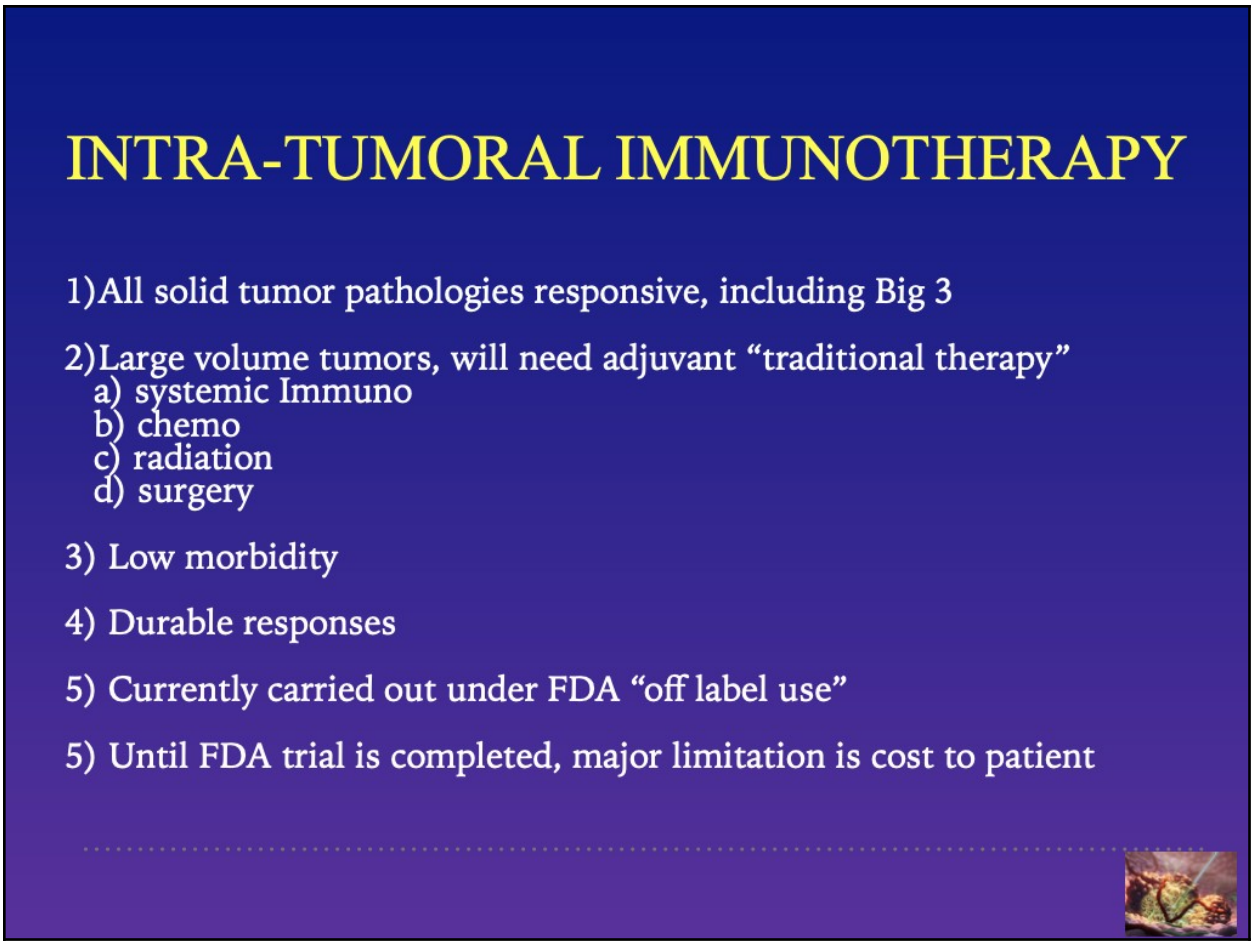


What can we say about this type of process?

It's an unusual treatment because it is unique in the history of cancer therapy, in that it is the first treatment that so far has worked on every tumor type we have tried it on. Usually, obviously, immunotherapy is tumor-type-specific because the big three don't respond to it. There is chemotherapy, which is tumor-type-specific, with different regimens for different cancers. We have found that every single tumor we have tried this on has responded. That's unique in cancer therapy.

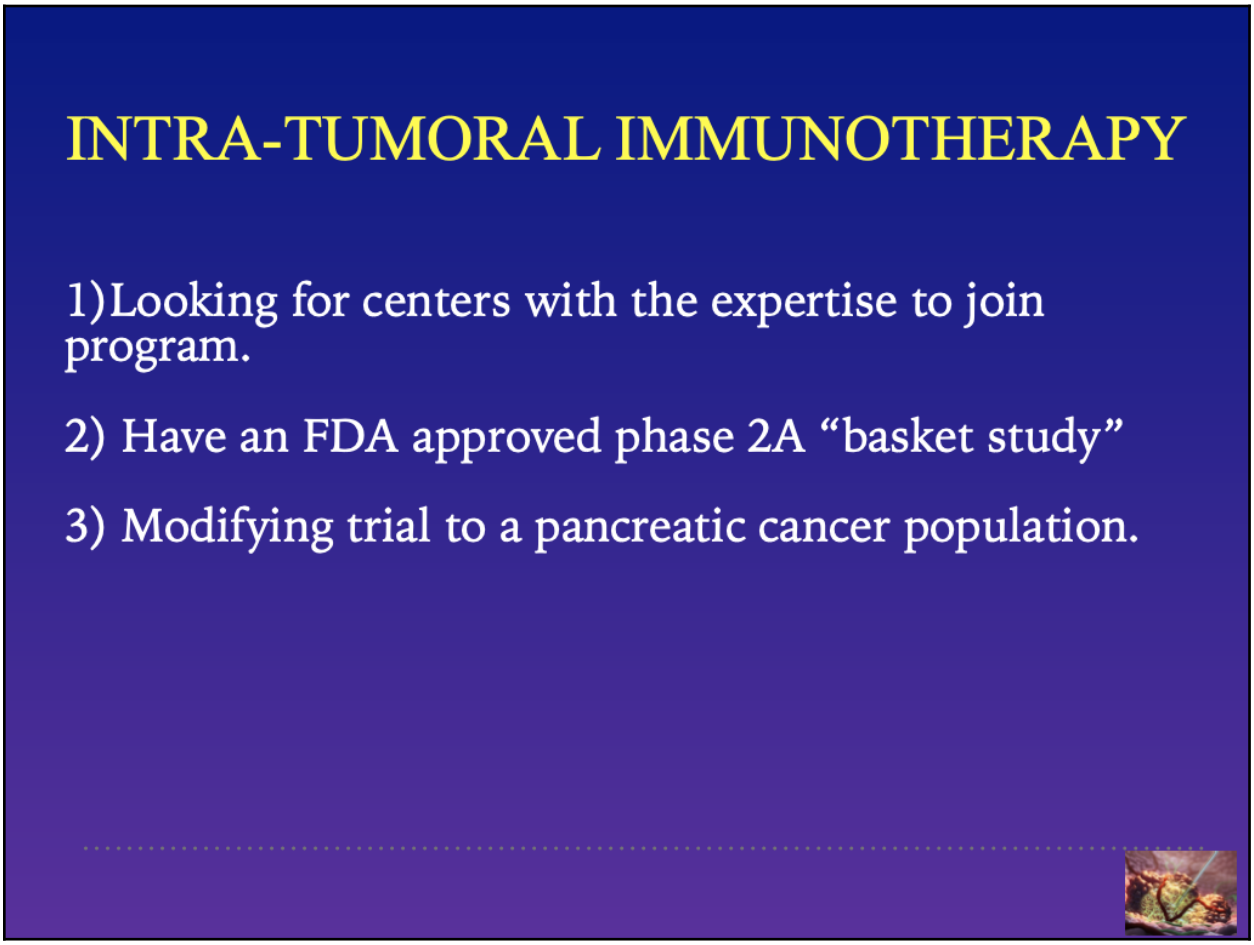
Large volume tumors will sometimes need adjuvant traditional therapy, or systemic immunotherapy. We try to stay away from chemotherapy, radiation, or surgery.

It has extremely low morbidity. We're not seeing the side effects that they see with traditional immunotherapy, we haven't seen any pneumonitis or hepatitis. We've seen one case in 200 that had some bowel inflammation that responded to treatment. A very low morbidity and side effects.

Durable responses. These responses, in my case, lasting for five years. Others have lasted many years. Right now, we don't know why.

Certain patients will need other therapies later on.

This is currently being carried out under an “off label use” in the terms of the FDA. So we're able to treat patients. Everything we're using is approved, but we're using it off label. So the FDA allows us to do that.



We have a trial that we're going to be carrying out. It was approved. We didn't have any money to accrue any patients. We are looking for funding now. We are hopeful that we will be getting it in the not too distant future. Our goal is to get this to patients as quickly as possible. That obviously means that we have to do FDA trials, and that's our goal.

We're looking for centers with expertise to join the program. We just added a center in Little Rock, Arkansas. We've got a center in Utah, and we've got a center in Florida. We've got three so far. We have an FDA-approved phase two basket study. That's that trial. It was a basket study. We were going to treat all sorts of cancers. But we've changed our focus to pancreatic cancer because we've been getting such remarkable results in pancreatic cancer. Those patients have so few options. If we have limited money, that's the group I think we should be working on.

Robert Gurmankin 23:31
You're using PDL-1 or PD-1 inhibitors, so that’s an immune checkpoint inhibitor. With any of these have you run into any issues with autoimmune disease?

Gary Onik 24:14
The autoimmune side effects that we've seen have been limited. The side effects that you worry about with usual immunotherapy, as I said, are pneumonitis, hepatitis, and colitis. We haven't seen those. We've had one possible case of colitis, although it wasn't classic. That's a question mark. But, let's say we've had one in 200, which is quite remarkable. The one thing that we worry about the most is myocarditis. We monitor patients very closely for that. We've seen one case of myocarditis out of those 100 patients. So that's very unusual. The thing we've seen the most probably is thyroid problems, and hypothyroidism. If that's the case, obviously, we monitor for that as well, and we'll do thyroid replacement. And usually, we're in good shape with that.

Robert Gurmankin 25:35
I had hyper progression with Keytruda even though I was MSI High and had a high tumor mutational burden and all. Does that mean that your approach might have something like that?

Gary Onik 26:08
We get genetic testing to see if there are certain genes that seem to indicate hyper progression. Usually we will give one treatment before we get that genetic testing. We're exploring ways of limiting the effective type of progression. Mark Taylor is working with us on that. Because you had hyper progression with systemic therapy, I'm not sure it necessarily relates to our therapy.

Brad Power 27:18
I'm a lymphoma patient, and I'm getting a cancer vaccine at the end of the month. Associated with that, something similar to what you were describing, is a drug called lenalidomide, and I was wondering whether you know that drug and whether that is also an immune system enhancer, similar to the ones that you're putting in that second step in your process?

Gary Onik 27:44
I'm not familiar with it. If you send me the information on it, I'll look it up, and consider it.

Ian Lewington 28:23
With a previous oncologist I tried to get in contact with you about 18 months ago, and we struggled to coordinate time zones. I've got a better oncologist now.

Because I've got advanced stage IV, Gleason 9 prostate cancer, a lot like yourself with multiple mets, going through chemo. What are the criteria for your treatment? I've had chemo, and I'm on the normal ADT, fairly low PSA at the moment, 2.5, and SUVs have shrunk down and around two, etc.

Do you need a certain size of tumor to start the treatment, or can you do it at any stage?

Gary Onik 29:18
If a patient is already on ADT, and they're tolerating it well, and they're not completely castrate resistant, meaning a rising PSA, we'll usually tell him to just stay on it until he is castrate resistant. Starting out, if you're newly diagnosed, you're better off trying it then than trying it as a first treatment. We have found that we can get some major responses and then either go on to something like Lu-177 and get a complete response, or have a patient who is going on ADT, but will get a better response and a longer term response from ADT.

One of the first patients we ever treated was a fellow with very widespread disease. His PSA was 1800 when we first saw him. He got a marked response. His PSA went down to 200, then started to rise again. Now we would have put him on systemic therapy, and he might have gotten a complete response. But the reason I'm telling you is that he went on ADT, and he's now going on nine years on ADT, and hasn't gotten castrate resistant yet. My experience is in patients with that kind of disease, they become castrate resistant pretty quickly.

That's a long-winded answer to your question: if your PSA is rising, I need to have something to measure basically. I don't want to take somebody off ADT if they've responded to it. So if your PSA is 0.5, and you have demonstrable disease on a PSMA scan, it doesn't have to be more than a centimeter or centimeter and a half to be useful for us to make a vaccine, then you might be a candidate.

Ian Lewington 32:15
My low point was 0.07. So I'm starting to rise, with my oncologist talking about going on to Abiraterone as the second line. I have multiple mets still based on a PSMA scan.

Gary Onik 32:40
Have you been on Enzalutamide?

Ian Lewington 32:43
No. My initial treatment was goserelin.

Gary Onik 32:45
Okay. So you haven't gone on second line therapy? If I was in that situation, I would have our treatment. And then if it didn't work, go on the second line therapy.

Ian Lewington 33:08
Okay. I might contact you separately. I have your contact details.

Allen Morris 33:43
[My apologies: I joined late and was at work, being interrupted, so I did not hear that Dr. Onik had largely already laid the following out].
On your formula: I've divided it into three components: (1) the cryosurgical (cold) lysis (breaking down of the membrane of a cell), (2) you inject Leukine (immune system stimulator) into the

bed, and (3) you give immune checkpoint inhibitors. I presume you must give that the same standard way, which is subcutaneous and intravenous , respectively? Is that correct?

Gary Onik 34:25
No. We give it all into the tumor.

Allen Morris 34:29
That is impressive. Now, as far as cryosurgical lysis goes, I imagine you could not possibly do that to bone mets, which are the most common mets in prostate cancer patients. Is that correct? You cannot do cryosurgery on bone, can you?

Gary Onik 34:51
We do bone mets routinely.

Allen Morris 34:56
That's interesting because you want to pick something that has a relatively large volume, so that you will get a relatively large volume of neoantigen release. I imagine, that unless the bone is fractured, the actual tumor volume for an isolated bone met would be relatively small. Is that not the case?

Gary Onik 35:23
No. Basically, we make a standard cryosurgical lesion, or freezing lesion. It's only about a centimeter in diameter. It's a very small lesion. It's not really a problem that way.

Allen Morris 35:48
I'm going to try my own formula for auto vaccination. I just coincidentally happen to be going into a “second” BCR (biochemical recurrence). I plan on getting a PSMA PET scan. I am hoping it's going to light up only a few bone mets and thus qualify as “oligometastatic”. If so,
I'm going to go the SBRT route (Stereotactic Body Radiation Therapy), a type of radiation therapy that uses many beams of energy carefully targeted to focus on growths of cells), probably the Proton flavor that I have already received from Dr. Carl Rossi, as opposed to cryosurgery.
I think you suggest that you believe cryo, theoretically, should be a better lysis technique than radiation therapy. That somewhat flies in the face of my understanding, the conventional wisdom, that radiotherapy is actually in and of itself, an immune sensitiver. Do you not believe that?

Gary Onik 36:37
I've read that it is, but nobody can show me any consistent data to really prove that.

Allen Morris 36:48
My understanding is that the abscopal effect was largely described in the context of Radiation Therapy, usually SBRT treatment whether by conventional photon or fancy proton energy.

Gary Onik 37:04
If you look at our patent, we have a whole bunch of ways that you can do the same thing.

If you are going to do that, I urge you to do it with intratumoral injection to the lesion because getting SBRT plus systemic is not going to do it.

[AM comment: Well Provenge works and is systemic only,
admittedly not to do the degree of your technique. But Provenge was never optimized. It is still generation 1.0.

And if your secret sauce is truly the intratumoral delivery, then I agree, SBRT certainly does not do that in and of itself. I would have to get someone to do a separate, intra bone injection. Dr. Rossi does not do that, nor I suspect any other Radiation Oncologist. But if anyone knows of one, let me know.

But SBRT per the abscopal (vaccine) effect, barring ADT which conventional wisdom views as an immune adjuvant, has never been optimized with other agents/adjuvants.
Stated another way, no one is giving immune adjuvants routinely to SBRT patients to optimize the abscopal effect, for example Leukine and low dose cyclophosphamide, among many others.

So, there is no apples to apples comparison of freezing vs. radiation as the secret sauce agent, in and of itself.

A scientific question is how do you experiment with your spectacular treatment to dissect out; Is it the cryotherapy, Is it the direct injection of Leukine, Is it the direct injection of ICIs, Is it the direct injection of double ICIs, that is the secret sauce, or is it as you presume, that the whole formula is necessary for success?]

Allen Morris 37:45
If I could drill down more on the Leukine. I saw your formula was 30 daily subcutaneous doses. Can you tell me what your dose is for subcutaneous Leukine?

Gary Onik 37:57
It's a standard dose. It's up to 250 micrograms per day.

Allen Morris 38:02
The actual dosage is 250 micrograms per square meter, and the average man is 1.9 sq.meter. So the standard dose is actually 500 micrograms. Am I wrong on that?

Gary Onik 38:19
No, you're not wrong. We have found that this amount works. We can tell by the response in terms of the patient's white count going up, and Leukine is just too expensive to use that way. We intratumorally use it at 500. Systemically, we use 250.

Allen Morris 38:58
Where do you inject the subcutaneous Leukine?

Gary Onik 39:01
Anywhere.

Allen Morris 39:14
I missed the ADT (androgen deprivation therapy) discussion. It's very much conventional to give ADT especially in the context of SBRT, which I think you're recommending against. The notion is that ADT is also an immune adjuvant. What is the ADT usage vis a vis your cryotherapy concept of autovaccination, immunotherapy?

Gary Onik 39:44
If a patient is on ADT, and they're doing well, we just suggest they continue on ADT until they become castrate resistant.

Allen Morris 39:51
It’s not part of your protocol for prostate auto vaccination in particular?

Gary Onik 39:56
It screws us up because we don't have a measure of how things are going.

Allen Morris 40:05
I found it fascinating that in your pancreatic cancer case that you effectively got what is seemingly a cure, or at least a long disease free survival for the liver mets. But there was a recurrence in the pancreas. That's fascinating to me because the exocrine pancreas, I believe, should be immune-privileged. And in fact, pancreatic cancer, specifically the most common type PDAC, a cancer of the exocrine pancreas, is considered a cold Tumor.

[Background: The exocrine pancreas makes one’s digestive enzymes. This is in contrast to one’s endocrine pancreas which among other things makes insulin. Concerning the latter, the corresponding disease state is called Diabetes Mellitus, that everyone is well aware of.

Back to the exocrine pancreas: You would not want your digestive enzymes released into your body, because if they were released, one would in essence digest oneself. In fact, acute pancreatitis, the condition wherein a significant amount of enzymes are released, is serious with a mortality rate of 10%. Indeed, acute pancreatitis results in a unique type of necrosis (cell death), called saponification. Because of this peculiar vulnerability, evolution teleologically would have favored those who would not develop autoimmune disease of the exocrine pancreas.
This is in distinction from autoimmune disease of the endocrine pancreas which is the cause of Type 1 Diabetes formerly known as Juvenile Diabetes. This type of diabetes is way, way less common than Type 2 Diabetes which is very common and, as you all know, is a scourge in the

“A Novel Immunotherapy Approach for 'Cold' Cancers” (Gary Onik, MD) [#86]

U.S. Whereas autoimmune (exocrine) pancreatitis is very rare. So rare, that the nosology of autoimmune exocrine pancreatitis is questionable.
The anecdotal, N of 1 case, of Dr. Onik’s who got complete resolution of the liver mets, suggesting that his autovaccination tumor lysis technique, elicited an effective T cell vaccine, somehow did not completely eliminate the pancreatic focus. Is this evidence of immune privilege?
And if so, has pancreatic immune privilege ever been demonstrated before?

I'm speaking to an evolutionary teleological (relating to or involving the explanation of phenomena in terms of the purpose they serve rather than of the cause by which they arise) explanation for why your pancreatic cancer patient would recur locally, but effectively cured systemically, specifically in this case, the liver.]

[AM Editorial: “18 prostate cancer patients, 50% had a complete response.” Patients with other cancers, such as pancreatic cancer, also showed encouraging results. Of six patients with non-prostate cancer: 33% had a partial response.”

Geez: Though, the series was small. I will make one conclusion. The OMG result is 50% complete remission in Prostate Cancer. Wow. And the 5 years +, no evidence of disease NED in Dr. Onik himself. Wow. You can not write a better Cancer miracle story..

So, the conventional wisdom of vaccine experts is that the hot tumor is the best tumor to develop a vaccine for. We heard this in the Dr. Sartor learning session.

Now, we have additional evidence from Dr. Onik, that what Dr. Sartor stated, though the conventional wisdom, and what you will read ad nauseum, is simply not true.
Dr. Onik’s limited data supports my contrarian theory, that prostate cancer, the prototype of a cold cancer, is the best cancer to pursue a vaccine for.
Give my theory a read, if you have the time. Forgive me it is still a work in progress. It is at the end of the Dr. Sartor learning session.

So, Dr. Onik is pursuing a study of his treatment on pancreatic cancer patients, a noble cause. And results will be more obvious in this patient population because of their unmet need, but Immune privilege of the pancreas itself, I believe, will have to be overcome.]

Gary Onik 41:15
Yes. There is a lot that we do not understand. We're finally working with a Department of Clinical Immunology down here in Florida, Nova Southeastern University. Once again, we're looking for funding to do that. When I came up with this, I took a good guess, partly from experience over the years, since we've been looking at this stuff for a long, long time. But we need to understand why some patients do well and some patients don't. If you have only a 40% success rate on average, why did the 60% not do well? If somebody like me lasts five years, if somebody like our first patient lasts eight years, but another patient gets a recurrence in two years, why is that? These are all things that we have to find out about. We’re at the very, very

beginning of this. In five years, we're going to know so much more about this, and hopefully be a lot better at it than we are now.

Amit Gattani 42:41
With a solid tumor, like my bone mets, I've always heard that it is very hard to get to the solid tumor. When I went through the procedure, the two tumor sites that Dr. Onik chose for me were the prostate itself and in the pelvic bone. I had no discomfort and no issues related to the surgical stuff that he did. This was the first time somebody got into the bone to do this for me. Kudos to Dr. Onik and his ability to get into the bone mets.

Continuing the discussion of SBRT and cryoablation: some other doctors who are working on this stuff use heat instead of cold. Can you comment on the effectiveness of your cold cryoablation approach versus the heat approach?

Gary Onik 44:18
Heating just doesn't make that much sense in this setting, because it’s denatured proteins. It's like you're going to cook a steak. It doesn't look like, “Good. The steak went into the oven.” Whereas with freezing, you can freeze the steak and thaw it out, and it looks like a steak. Heating does not make sense in this setting. That's my take on it. I wouldn't expect that long term those results will pan out. But who knows?

Paul Van Camp 45:27
On X-ray SBRT to release antigens into the blood to try to stimulate an abscopal response: I recall Beyonda (?) in Australia was being touted as an agent that could produce a body-wide response after radiation of just one lesion. But now that seems to have disappeared. I don't hear about it anymore.

I'm wondering about the use of some systemic immune cocktail after your treatment to try to augment a more body-wide response.

Gary Onik 46:24
We are always open to improving what we're doing. Some of the things that we are doing now, were suggested by patients, that we can incorporate it into our treatments. Our goal is to get this out there, even if in its present form. It's not perfect. Because we really think that it can make a big, big difference for thousands, if not tens of thousands of patients. At some point, you have to say, “Okay. This is what we're going to test for. There may be something better. We may be able to improve it, but we have got to test something. This is what we're going to test.” We pretty much have our system down.

One of the things that we haven't talked about is something that we have added in the last couple of years, which is the use of low dose cyclophosphamide to deplete the T reg cells, that was not used in our study. I guess I didn't speak about it, but we're now doing that on a routine basis.

Brian McCloskey 48:02
You talked a little bit about customization of the immunotherapy itself. How do you do the customization? Are there certain types of diagnostics that you use, or would use, to customize the immunotherapy? For example, we have partnerships with many different companies. Gitte Pedersen is here, representing one of those. We can get access to proteomics. We can get access to spatial phenotyping or lots of different tests. What would be helpful, if anything at all, in customizing the immunotherapy cocktail?

Gary Onik 48:48
I think anything that we can do as we go forward, for instance, to look at the proteomics. One of my greatest strengths is my ignorance. I don't know anything about proteomics, but I know that it's been brought up, and we've discussed it with experts a number of times in terms of being able to see if we can customize the procedure.

We're going to be doing a trial. We're going to have tissue. We're going to have blood samples. We're going to have all of those things. We would love to track anything that anyone would want to look at, to see if it can make an impact on the treatment, or in the designation of who will do well and who wouldn't do well. We don't want to be doing procedures on patients if it's not going to do well. It's just a waste of everyone's resources and time.

But there are some caveats to that. When we started going to next gen (sequencing), and looking at expression of the checkpoints in the tumor, we felt that we could improve our results by excluding patients that did not express to a high level those checkpoints in their tumor. Sure enough, in retrospect, looking at how the data panned out, however, we did have a number of patients who got wonderful responses and didn't have the checkpoint expression that you would expect to make them successful. We found that we couldn't use it clinically as an exclusion criterion, to say to the patient, “Look: Don't waste your time. Don't waste your money. We can't do that.”

[AM Editorial: I apologize, but I couldn't help myself from interjecting.
This above Dr. Onik paragraph speaks to how the conventional wisdom that the hot tumor (the tumor with high tumor mutational burden (TMB) and high Tumor infiltrating lymphocytes (TILs) is the best candidate for a vaccine is wrong.

Background: The hot tumor is the most genomically advanced tumor: one that is high in PDL1 expression, TILs, high Tumor Mutational Burden, etc., that everyone expects to be the best responder to immunotherapy because of the Immune Checkpoint Inhibitor (ICI) revolution.

There is a simple disconnect. No one is separating the concept of

1. Immune checkpoint inhibition and immune adjuvant (e.g.historic IL-2) type immunotherapy which is most certainly better in the hot tumor from
2. Vaccine type immunotherapy.

They are 2 different things which work by 2 completely different molecular mechanisms.

And simply, my contrarian theory is that a vaccine will work best in a cold tumor.
And Dr. Onik’s limited data and the Provenge data, the only successful therapeutic cancer vaccine to date, support the notion that the earlier the better in the genomic evolution of a cancer, which also corresponds to the colder the better. Another fallacy, at least with respect to Prostate Cancer, is that we have to make a cold tumor, hot.
At least do not do this by trying to genomically advance it, especially with dsDNA breaks.
By all means make the tumor hot, the way nature has been curing cancer, since the evolution of the jawed chordates 100+ million years ago, by vaccination.
If you don’t believe me, just ask the Sea Gar, and there is a Cuban Sea Gar.]

But we're willing to look at anything that anybody wants to study in our patient population to help us figure out who's good, or how we can improve it. We'd love to do that. We want to know as soon as possible, so we can get it into protocol, because the protocol is being written now.

Amit Gattani 51:25
We have a list of partners that we will be happy to share with you. It will be updated on our website in a week. If there's a particular partner that you would prefer us to connect you with, we'll be happy to do that.

Gitte Pedersen 51:51
We should talk. We are doing RNA sequencing. It’s obviously very complicated, and certainly not to be relied on as just one biomarker to make treatment decisions.

This is the innate immune system functioning. Are the MHC (Major Histocompatibility Complex, which codes for cell surface proteins essential for the adaptive immune system) A class genes expressed? There are so many other things to take into consideration. I'd be happy to send you one of our reports. You can take a look.

Gary Onik 52:35
We've been talking only about the adaptive immune system here in terms of training the tumor to be recognized. But the innate immune system does have a very important role because it's the freezing that also damages the tissue and sends out those signals that say, “Hey! Something's been damaged. Come here.” That is an important aspect of what we're doing. We have no idea when we look at somebody's work whether they have a good innate immune system working or not. We'd love to talk to you.

Gitte Pedersen 53:23
I'm sure we can get connected.

Because we have been doing work in breast cancer, but now also in ovarian cancer and follicular lymphoma, do you have any experience with any of those two cancers?

Gary Onik 53:45

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Not lymphoma as of yet, and not ovarian cancer as yet either. The most exotic tumor we've treated was a glioma (a tumor of cells in the central nervous system), a glioblastoma (a highly invasive glioma in the brain), and we got a really wonderful response in that patient. So far, there has not been any particular tumor that has not responded to the treatment. We would love to try this on those types of tumors.

Gitte Pedersen 54:41
This is super encouraging, especially for the patients on this call that have not responded to the standard of care.

Amit, I sincerely hope that you will have a response to this treatment.