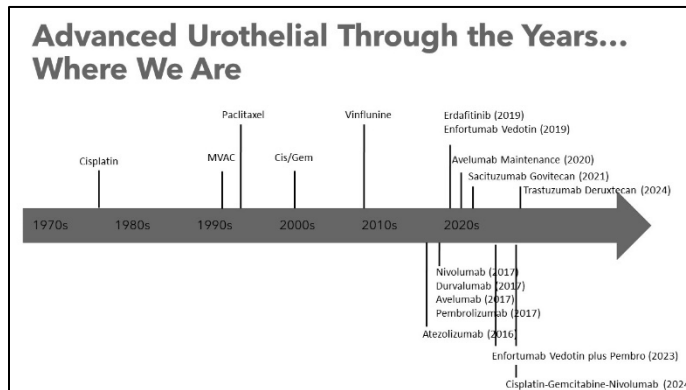


# Advances in Muscle Invasive and Metastatic Bladder Cancer: Past, Present and Future Directions

Guest Presenter:  
**Dr. Tyler Stewart**  
 Assistant Professor of Medicine – UC San Diego  
 Genitourinary Malignancies



**Dr. Tyler Stewart:**



This is where the landscape is now for advanced urothelial carcinoma. So right now, the two treatment options that I really think about is enfortumab vedotin plus pembrolizumab, and then maybe sometimes thinking about that combination of cisplatin, gemcitabine, and nevolumab.

**Dr. Tyler Stewart:**

**Therapies on the Horizons**

- New ADCs
- New immunotherapies
- New FGFR inhibitors
- And more...

I want everyone to know that there are new drugs and new therapies that we are investigating every single day. So all of us at academic centers and many non-academic centers as well, do clinical trials where we are investigating new drugs and new ADCs that are coming down the pipe.

I do think that the therapies that we have now have made huge gains, but there are new therapies that hope to do even better.

There are new immunotherapies. We talked a lot about those, these anti-PD-1 therapies, but there are other immunotherapies that are being studied, and there are new FGFR inhibitors and more. So

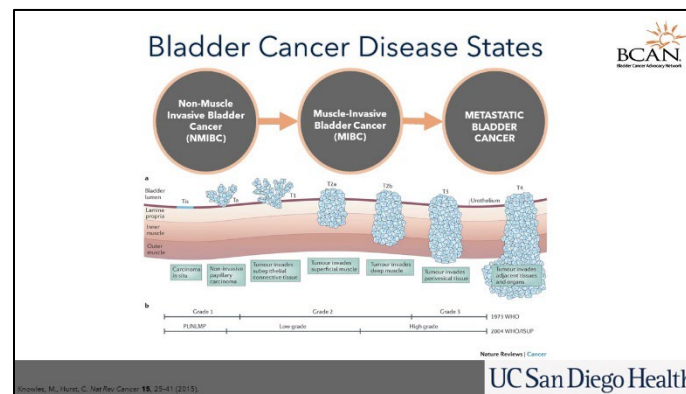
we are hungry to see these new therapies and see how they do, and really trying to make people live longer, happier, healthier, and increase cure rates.

**Dr. Tyler Stewart:**



When I see a patient who has localized cancer, what I think about is, can I use any of the medicines that I know can help people who have advanced disease, and can I improve the outcomes for patients who have localized disease?

**Dr. Tyler Stewart:**

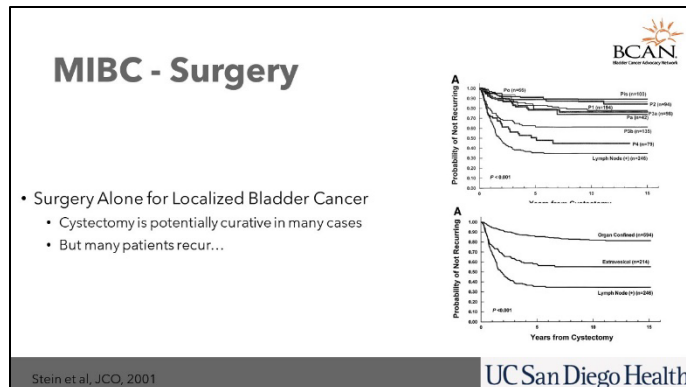


So as we discussed earlier, patients who have localized cancer, we treat them very different. So patients who have non-muscle invasive bladder cancer, again, sometimes that can just be scraped out, or sometimes we give something into the bladder to prevent it from coming back.

But for cancer that has gone into the muscle layer, that really represents a more locally advanced cancer, which can

have the potential to escape. Oftentimes, what we'll do for patients with muscle invasive bladder cancer, a standard treatment is to remove the bladder, trying to get all of that cancer out of the body before it spreads.

**Dr. Tyler Stewart:**



When we looked at outcomes for patients who have locally advanced bladder cancer, what we know is that surgery can be curative, but sometimes that cancer comes back.

**Dr. Tyler Stewart:**

### MIBC - Neoadjuvant Chemotherapy

• Neoadjuvant Chemotherapy → Surgery

- Grossman et al, NEJM, 2003
- 3 cycles MVAC (methotrexate, vinblastine, Adriamycin, cisplatin)

|                                       | Cystectomy Alone | MVAC x3 + Cystectomy | p-value |
|---------------------------------------|------------------|----------------------|---------|
| Number of patients                    | 154              | 153                  |         |
| No residual disease at cystectomy (%) | 15               | 37                   |         |
| Median OS (months)                    | 46               | 77                   | 0.06    |

*N Engl J Med 2003; 349: 859*

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In studies that were done now over 20 years ago, what we found was that when we gave chemotherapy for patients who have muscle invasive bladder cancer who are planning to go for a cystectomy, we asked ourselves, "Can we give them chemotherapy and get rid of any cancer that spread, and can that improve long-term outcomes?"

So a study was done here, where looked at giving chemotherapy before. And this study suggests that when you give chemotherapy before surgery, on average, you increase your chance of being cured. In a meta-analysis, the chemotherapy probably increases your chance of being alive at five years by around 5 to 10%. So there is a chance you can be cured by surgery alone, but chemotherapy probably increases that chance by around 5 to 10%.

And so for patients who are coming to see me today with muscle invasive disease, the major question is should we consider some chemotherapy before to increase those cure rates after surgery?

So when we look back at this, we know that when we give chemotherapy and then people have surgery that many patients can be cured. Some patients, that cancer comes back. And so after surgery, there are some patients who are at high risk of their cancer coming back.

**Dr. Tyler Stewart:**

### Adjuvant Immunotherapy

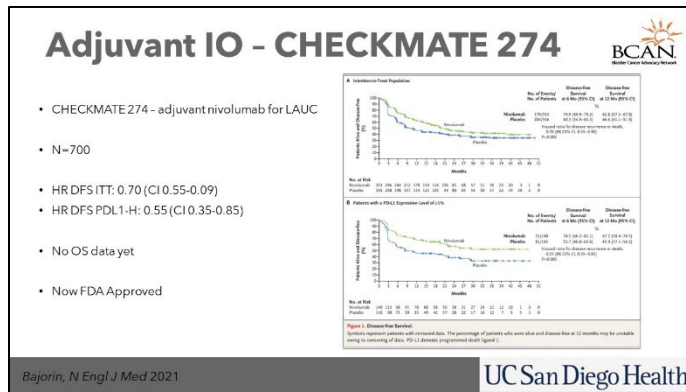
*Nadal R and Apolo A. Curr Treat Options in Oncol. (2018) 19: 36*

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Because of this, we did multiple studies looking at immunotherapies for patients after they receive a cystectomy. So patients after they have their out getting a checkpoint inhibitor. And there are three major studies that have been done. One was with a drug called pembrolizumab, one with nivolumab, and one with atezolizumab. And generally, all of these studies looked at, should we give immunotherapy right away or should we

just watch it?

Dr. Tyler Stewart:



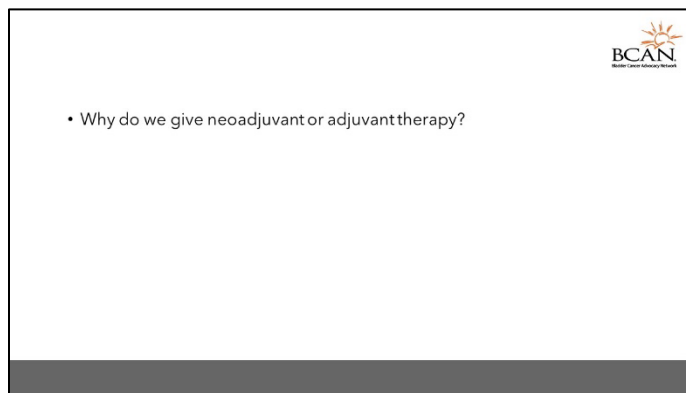
So the CheckMate 274 study was a study where half the patients after they had a cystectomy received immunotherapy, and half the patients did not. And the immunotherapy they received here was a drug called nivolumab.

And what this study showed was that in patients who got nivolumab, there was a lower rate of your cancer coming back. What we don't know yet is whether or not

this really improved overall survival. Really, do we have to give it right away, or can we wait until it comes back and then give it? Because if we give it to everyone, some of those patients are going to be cured with surgery alone, and may not ever require nivolumab.

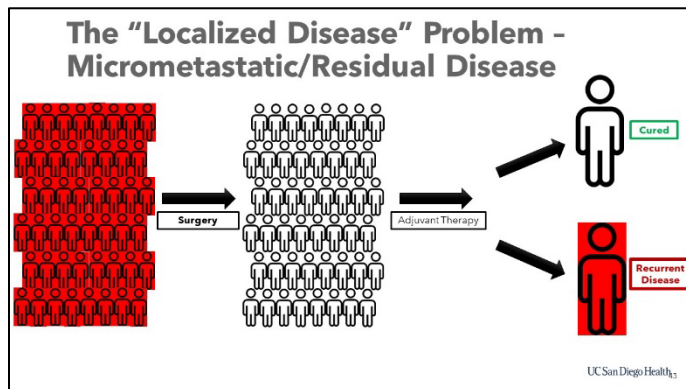
So we do really want to see what this overall survival data looks like. But the early data suggests that if you receive nivolumab, it decreases the rates of your cancer coming back. And because of this, this drug is now FDA approved to give for patients after a cystectomy who are at high risk of their cancer coming back.

Dr. Tyler Stewart:



But one of my interests and one key interest that I hope everyone is thinking is that, does everyone need this neoadjuvant and adjuvant therapy?

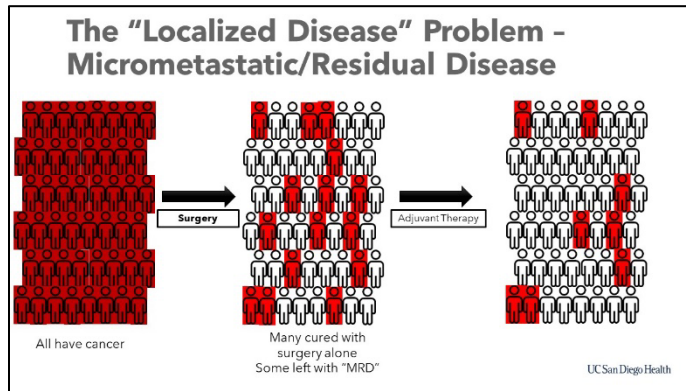
Dr. Tyler Stewart:



So here's how I think about localized cancer. Let's just say you come in and you have a cancer in your bladder. Patients come in, they have a cancer in their bladder, and then they have their bladder removed. They have surgery and they hope that they're cured. And then sometimes we give some immunotherapy

or something on the backend, and some people their cancer comes back, and some people their cancer doesn't. So how does that happen?

**Dr. Tyler Stewart:**



Well, it turns out that when cancer comes back, it's really because that cancer has already spread and we just don't see it. So although oftentimes we oncologists will get scans and say, "You're clear of cancer," sometimes that cancer is just too small for us to see. So after surgery, there are some patients where there is a small amount of cancer left, and there are many patients who are cured with surgery alone. And wouldn't it be nice if we knew who

had cancer still left and who actually needed more therapy, and which patients didn't need it at all?

**Dr. Tyler Stewart:**

**Can we identify patients with MRD?  
And how?**

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So how can we identify patients who have cancer still left? So this is a concept called minimal residual disease. A microscopic cancer that is left in the body, how can we see that?

**Dr. Tyler Stewart:**

**Circulating Tumor DNA (ctDNA)**

BCAN  
Bioscience Resource Project

- Cell-free DNA (cfDNA) refers to fragmented DNA found in the noncellular component of the blood
  - Circulating Tumor DNA (ctDNA) is only a fraction of cfDNA (depending on the type of, and amount of tumor)
- Clinical Applications
  - Qualitative:
    - Molecular Diagnostics
    - Tumor Resistance Mechanisms
  - Quantitative
    - Tracking Therapeutic Response
    - Screening General Public for Cancer
    - Guiding Systemic Therapy for Localized Disease

Is this a marker for residual disease?

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Well, one of the technologies that we are working on is something called circulating tumor DNA. So it turns out that in your body, your cells oftentimes will die and give off some of that DNA into the blood, and it will spread throughout the body. And in patients who have cancer, a small fraction of that will be cancer DNA.

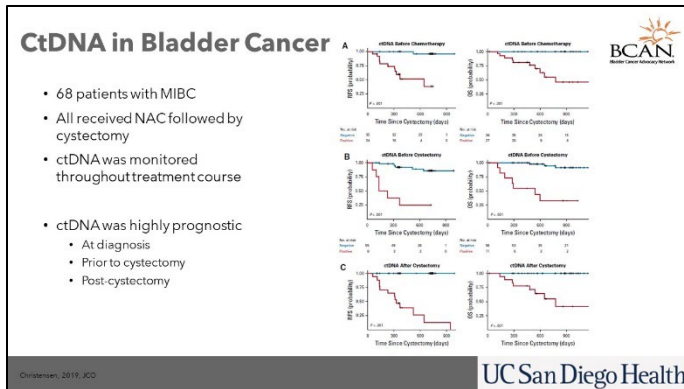
And as our technology has increased, we are able to find cancer DNA in the blood at

very, very low levels. And so many of us in the field are now thinking about this as, well if you have surgery, maybe we can look afterwards and see if you still have any of that cancer DNA in the blood.

And maybe that can direct us on who should get more, and maybe who should get less therapy on the backend.

What's important to know about this cancer DNA is that it's not just in plasma. Actually, we can find this in all sorts of body fluids. In urine studies, in plural fluids, actually in spinal fluids as well. If there's cancer there, then sometimes we can find cancer DNA.

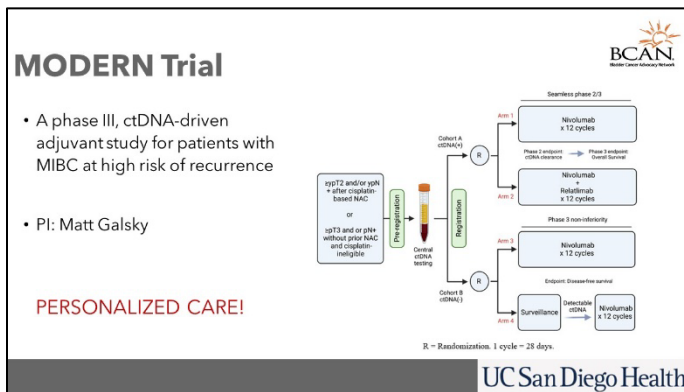
**Dr. Tyler Stewart:**



In a very, very important study that really helped push this field forward, a group looked at circulating tumor DNA in patients who had had cancer and had their bladder removed. And what they found is that after cystectomy, if your ctDNA was negative, rarely did those patients recur. Whereas if your ctDNA was positive, if we found that cancer DNA in your blood afterwards, nearly all of those patients had their cancer come back.

Really suggesting that that cancer DNA was really a sign that there is still cancer left over, and if left unchecked can come back and hurt a patient.

**Dr. Tyler Stewart:**



We are now in the midst of using this technology to personalize patient care. So although right now we do not use these tests to decide who should and who should not, because the data is not there quite yet, there are ongoing studies evaluating this.

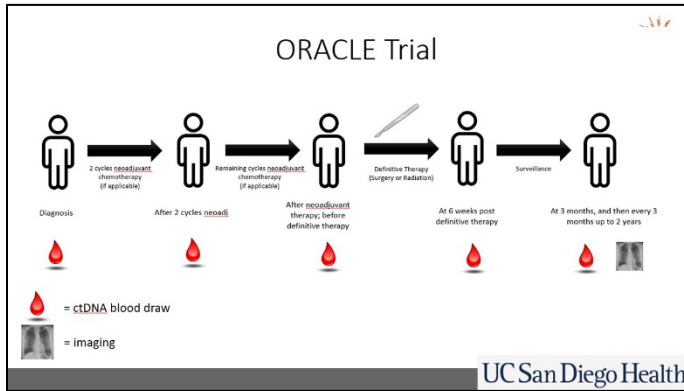
Here I'm highlighting something called the MODERN trial. This is a trial that I happen to be involved with, where we are taking

patients who have had a cystectomy to try to cure them of cancer. And then after that cystectomy, we are trying to decide who needs immunotherapy based on that circulating tumor DNA. Whereas if it's positive, well those are patients who we think are at very high risk of their cancer coming back. They probably have cancer left over. And we're actually studying whether or not we should give them just one immunotherapy. Or maybe because they're such high risk, we should actually give them two immunotherapies with nivolumab and something else called relatlimab, which is a LAG-3 inhibitor.

But in patients where that ctDNA is negative, they are being randomized to nivolumab, which we would consider a standard of care, or just watching their ctDNA status, and only giving that nivolumab if their ctDNA becomes positive.

I personally think that these type of therapies and these types of trials are revolutionizing cancer care. And I'm really trying to ask the question, who needs therapy and who does not? And escalating the therapy if needed for the patients who need it and de-escalating therapy for the patients who do not need it.

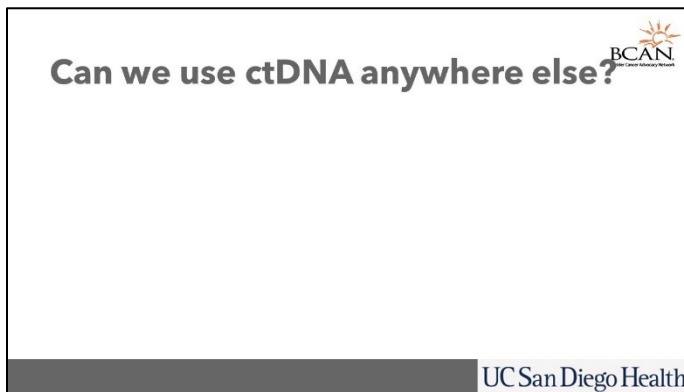
**Dr. Tyler Stewart:**



There are some ctDNA tests that are around already, but there are new ctDNA tests that are being investigated using different methodologies. So the way that we track if somebody has cancer left in the body right now is often through something called PCR, and there are different methodologies that are being investigated that can be even more sensitive, that can really discriminate who is most likely to have cancer and who

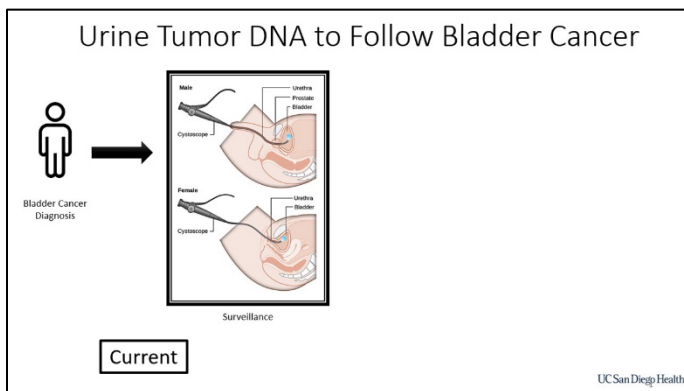
does not. And we're excited to be a part of some of those studies here at UC San Diego.

**Dr. Tyler Stewart:**



One of the things that I'm very interested is, can we use ctDNA anywhere else? And if you're thinking about bladder cancer, you got to be thinking about something else, and that is urine.

**Dr. Tyler Stewart:**

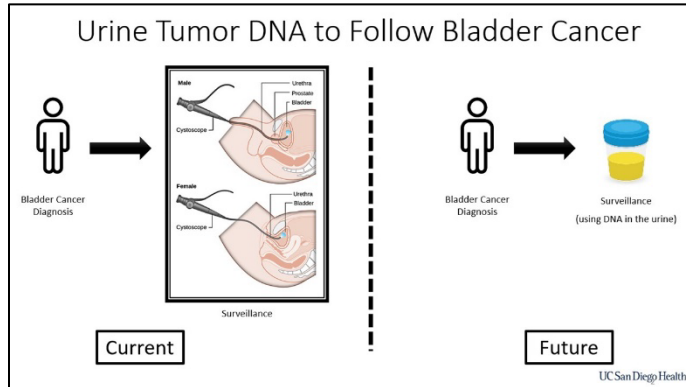


And can we use urine tumor DNA to follow patients with bladder cancer?

So right now, as many people on this call might know, in patients who have bladder cancer, oftentimes what we'll do is especially if they have superficial bladder cancer, we might go in there, resect that cancer, and then sometimes give them BCG or just watch. And what we'll have to do in order to investigate if their cancer

comes back is we do these cystoscopies every three months to see if their cancer comes back. Those cystoscopies are invasive, and they're not fun, and nobody likes to do them, and nobody likes to have done on them.

**Dr. Tyler Stewart:**

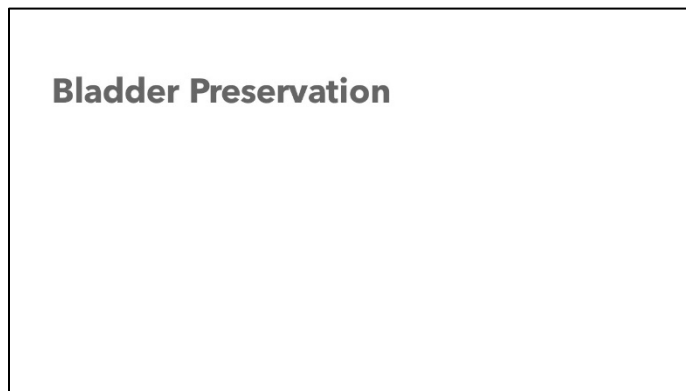


So wouldn't it be cool if instead, we could just have you pee in a cup? And if that urine could really tell if there's cancer or no cancer in there, maybe we get to avoid a cystoscopy or maybe it's less cystoscopies for a year.

So our team is very excited. Many teams are very excited about this out there, and I think that these tests are in the future. I think five, 10 years from now, these are

really going to be used all the time in clinic. These are still in investigation right now. We're still running clinical trials. They're not there yet, but we're getting closer and closer.

**Dr. Tyler Stewart:**



Bladder preservation is a huge interest of many of us who treat bladder cancer. So especially patients who have muscle invasive disease, the standard or at least a standard of care is to treat patients by taking their bladder out. And what we might ask is, is there any way that we can treat the cancer, get rid of all the cancer, but preserve that bladder?

**Dr. Tyler Stewart:**

One of the ways that we do this currently is something called chemo radiation, where we use radiation and a small dose of chemotherapy that actually weakens the cancer and makes that radiation more effective.

And what we know is that chemo radiation is a very effective method for many patients who have muscle invasive bladder cancer. And what we know is that

there are more and more radiation novelties and new techniques that are being developed that can

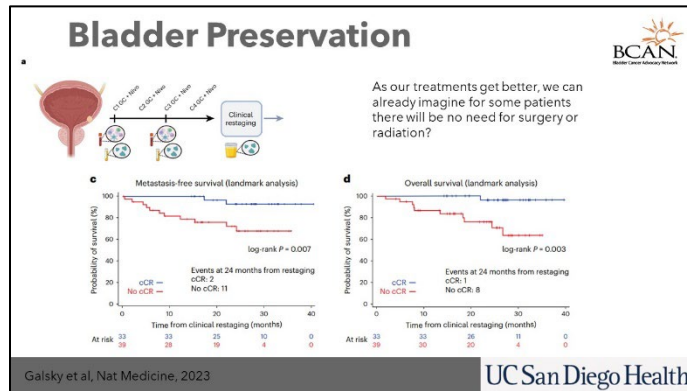


make it more efficacious and less toxic. So less damage to the bladder and surrounding areas, but more likely to kill the cancer, and those are being investigated.

We are also doing studies right now, for instance, the SWOG 1806 study, which is chemo and radiation, versus seeing if the addition of immunotherapy can actually improve those long-term outcomes.

This study is actually all enrolled. It was a national study that we're very excited about, and hopefully we'll find out the answer of whether or not immunotherapy can increase those cure rates in the next couple of years.

**Dr. Tyler Stewart:**



The other thing that we can think about is as our systemic therapy gets so much better with these new drugs that we are talking about, could there be a case where we could just treat somebody with medicine, and not have radiation, and still try to cure somebody's cancer? These types of studies are already being done.

This is just one study that was done by Matt Galsky and his team that looked at

patients who had muscle invasive disease, treated them with chemotherapy and immunotherapy. And if all of that cancer was totally gone from the bladder, they were just watched, and many of those patients actually did very well for a long time.

This study is just novel and absolutely not primetime, not ready for clinical, to be done in the clinic, outside of a clinical trial just yet. We need more patients. We need to have further investigation for this. But it is very exciting to think about a day when we might be able to just give medicines, treat somebody who has locally advanced cancer, and maybe cure them without getting their bladder out or even radiation.

**Dr. Tyler Stewart:**

**We've made progress... but not enough**

- More therapies to help people live longer, happy, healthier
- Need treatments that can cure
- Need therapies to help patients keep their bladder
- More precision therapy - escalating therapy for those who need it, and holding therapy for those that don't
- Methods to monitor patients less invasively, improve quality of life - thrive beyond bladder cancer

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I want to end on this note. So we've made progress, but it's not enough. So through efforts here through BCAN, we are working really hard to try to increase the therapies and the agents that are available to make people live longer, happier, healthier lives.

And ultimately, what we are looking to do is we are looking to cure patients, cure patients with advanced, locally advanced disease. Trying to keep their bladder and

making therapies more precise, finding out who really needs it, and giving therapy to those who need it, and holding back therapy for those who would not benefit.

And then I do think that we need methods to monitor patients less invasively, improve quality of life. We want patients to not just live with bladder cancer. We want patients to thrive beyond bladder cancer. We want patients to have great qualities of life and leave that bladder cancer behind.

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