

SURVEILLANCE AND RECURRENCE

With Dr. Eila Skinner And Dr. Yair Lotan

Recurrence

Dr. Yair Lotan: What about recurrence?

Dr. Eila Skinner: One of the things I wanted to address is why sometimes after you've had your initial tumor resected, your doctor will say, "Well, we need to go back and do it again," and that's becoming more common now and it's been recommended in a lot of situations. Part of the problem is it's difficult for the urologist to tell how deep they're going when you remove one of these tumors, and sometimes we don't actually get muscle in the specimen. In that situation, especially if the tumor looks like it's starting to invade, we want to go back and make sure that we get a deeper piece to know whether or not it's going in the muscle. Patients sometimes with a big tumor or multiple tumors, we can't be a 100% sure that we actually have removed all the tumor, and so we may go back again.

WHY MIGHT YOU NEED A REPEAT TUR?



- It is hard for the urologist to tell how deep they are cutting doing a TURBT
- Ideally we want to sample the muscle layer under the tumor
- We usually recommend a repeat TUR/Biopsy in three situations:
 - Any patient with lamina propria invasion, even if there was muscle in the specimen
 - A patient with big or multiple tumors where the surgeon feels they might not have removed all the tumor
 - In some patients with high grade Ta tumors when there was no muscle found in the specimen
- Repeat resection/biopsy has been shown to more accurately identify muscle invasion, avoid undertreatment, and improve outcomes with BCG

Basically, this repeat resection has really changed a lot of aspects of bladder cancer especially in more high-risk patients where we think we can do a better job of figuring out whether there is microscopic invasion of the muscle and whether it's safe to do intravesical therapy for those patients.

Dr. Eila Skinner: I wanted to talk a little bit about Blue Light Cystoscopy because some of you have already asked about that. This is a technology that has been available for a few years, but it's not widely disseminated yet. Basically, what is involved is that a liquid called Cysview is put into the bladder about one hour before the resection or before the surgery. The liquid doesn't hurt or it doesn't really cause any reaction. It's basically just put in with a catheter. Then when the patient is asleep and we're looking in the bladder, if we flip the scope to a Blue Light instead of white light, it'll make the tumor shine like you can see on that picture on the right.

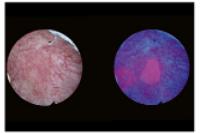
BLUE LIGHT CYSTOSCOPY

Cysview is put into bladder 1 hour before the TURBT.
At surgery a special cystoscope with blue light is used
Tumor "lights up" pink.

Helps urologist see small tumors not easily seen on white light
and better at seeing CIS

- Most helpful if multifocal cancers or no visible tumor with positive cytology
- Shown to decrease recurrence

▪ Problem - requires expensive new equipment





It's helped us see tumors that are too small to see under white light. It seems to be better at identifying where there might be this carcinoma in situ. I find it particularly helpful in patients with multiple tumors and also in patients, like Dr. Lotan was talking about, where we have a positive cytology, but we can't actually see a tumor. Part of the reason that this is not widely available is that it is expensive. It's about a \$100,000 investment for the hospital. So it just takes time for hospitals to make the decision to invest in that. But it is something that I think is becoming more widespread and more urologists are becoming comfortable with it.

The chance that cancer will come back? We know that bladder cancers do tend to come back, that's the natural history of them, but the risk of that varies. We divide patients into these low, intermediate, and high-risk categories. There's a lot of different systems for doing that. This is just the one that I think is the simplest. But if somebody is low risk, which means a small tumor that is low grade, they have a chance of recurrence, but it's probably around 50% over the next three to four years, but the chance that the cancer is going to spread is close to zero.

WHAT ARE THE CHANCES OF CANCER COMING BACK?

| Low Risk | Intermediate Risk | High Risk |
|--|--|--|
| Risk of Recurrence: About 50% Risk of Progression: Close to 0 | Risk of Recurrence: 50-70% Risk of Progression: About 10% | Risk of Recurrence: > 70% Risk of Progression: >20% |
| Office fulguration Less frequent cystoscopy Post-TUR intravesical chemotherapy | Induction (6 week) intravesical chemotherapy (MMC, gemcitabine) or BCG +/- maintenance | Intravesical BCG plus maintenance Consider early cystectomy |



In that situation, if it comes back, we will use for example office fulguration where we just burn the tumor in the office or, perhaps, look in the bladder a little less frequently since we're not so worried about it. And there's also a role for using chemotherapy right after the initial resection, and that's been used. That's been shown to reduce recurrence as well.

The intermediate risk patients have a higher risk of recurrence and also a little bit higher risk of progression. Those are the patients, for example, with multifocal low grade tumors or small high grade tumors and that are on the surface. Those can progress at about a 10% risk.

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For those patients, we think it's important to use more than just that single dose of therapy. We actually recommend what we call induction therapy. For this group of patients, you can use BCG, which Dr. Lotan is going to talk more about, or you can use other forms of chemotherapy like Mitomycin or gemcitabine. They're all put in in the office once a week for six weeks. Then there's various maintenance schedules that might be used afterward.

Then the last group are the patients who are at the highest risk of progression. Those include the patients with carcinoma in situ or high grade T1 or large high grade TA tumors and also includes patients with weird histology. There's a bunch of unusual histologies that fall into that category. For those, we think BCG is the first choice and really should be used, unless there's a contraindication to it, and for those patients also, we're more aggressive at recommending that you consider cystectomy early because we know those can progress if we don't or if we're not effective in using BCG.

CAN YOU PREVENT RECURRENCE ?

BCAN. Bladder Cancer Advocacy Network

- STOP SMOKING !!
- All of these have been studied with outcomes that are either negative or ambiguous results:
 - Water intake
 - Vitamins
 - Selenium, other minerals
 - Retinoic acids
 - Alkaline water
 - Fruits and vegetables
 - Exercise

A Recurrence-free Survival graph showing survival probability over time (months) from 0 to 84. The y-axis ranges from 0 to 1.0. Four curves are shown: Quitters (red), Ex-smokers (green dashed), Non-smokers (blue), and Continued smokers (cyan). The Quitters and Ex-smokers curves are significantly higher than the Non-smokers and Continued smokers curves, indicating lower recurrence rates.

Dr. Eila Skinner: I often get this question from patients. Can you prevent a recurrence? What can I do to decrease my risk? The first thing is to stop smoking, if you still smoke, because we know that patients who continue to smoke have a higher risk of recurrence and, if you quit, even if you're 78 years old, you can actually reduce the recurrence rate. If you need an incentive to stop smoking, just think that every cigarette is going directly to your bladder and making it mad, so I think it's important.

The frustrating thing is all these other things have been studied, vitamins, selenium, retinoic acid, alkaline water, fruits and vegetables, and exercise. None of them have been convincing that you can actually impact the risk of recurrence. I think eating a heart-healthy diet makes sense, so, whatever you eat that's good for your heart will also be good for the cancer, but there's not one pill that I would recommend that has been shown to make a difference.

Most of the studies with vitamins, unfortunately, have shown that if you have a diet that's high in vitamins is good for you. If you tried to do it with a pill, it hasn't worked, so we don't generally recommend vitamin pills for patients for this kind of cancer since they haven't been proven. Again, just eat the diet that's good for your heart.

CAN YOU PREVENT RECURRENCE NUTRITION?

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- Most studies of vitamins and cancer have shown that vitamin pills can't replace a healthy diet
- **Recommendation:**
Eat a diet that is good for your heart!!

Dr. Yair Lotan: Dr. Skinner very nicely outlined the fact that a lot of patients are at risk for recurrence, and there have been several types of therapies that have been developed to try to reduce the risk of recurrence. They really broadly fall into either immunotherapy or a chemotherapy that we put in the bladder.

The main immunotherapy that's been used, in fact, over 40 years now is BCG. BCG is an attenuated form of tuberculosis, but it still has a little bit of the live tuberculosis. The way we think it works is that we think that it tricks your body's immune system into thinking that your bladder is being attacked by tuberculosis and the immune system comes to fight it. It gets there. There's very little live tuberculosis. Most of it is dead, but it finds cancer cells and attacks them.

Chemotherapy is very different than the chemotherapy we give you through the vein in the sense that the bladder is designed not to absorb fluid. Otherwise, you'd make urine and reabsorb it and have to make it all day. You can put fairly toxic chemotherapy in the bladder and not have the same side effects that you would by putting it in the vein because it does not get absorbed. The problem is, because it does not get absorbed deeply, the chemotherapy really is most helpful for cancers that are very much at the surface. If you have cancers that are going deeper, the chemotherapy probably will not get there.

In Europe, they have developed some types of treatments where you heat the chemotherapy or use electricity to try to drive it into the tissues more. Those are not approved in the United States. At this time, we're really limited with how we give chemotherapy just by putting it in there. It's usually given through a catheter and held for an hour or two by patients and usually wait two to three weeks at least after the initial resection to allow the lining to heal enough so you do not have systemic absorption.

Who do we give the treatment to? Anybody who's at high risk for recurrence. We're really looking at usually high-risk patients or intermediate risk patients. Those are patients who've already shown signs of recurrence or have multiple tumors, those at high-risk for progression, patients with carcinoma in situ which fall into both groups, high risk for recurrence and progression and, very rarely, we give it into patients who have residual cancer and mostly with patients with very small tumors or patients who are at very high risk for surgery.

ADJUVANT INTRAVESICAL THERAPY



- Intravesical therapies are used to reduce risk of recurrence
- Bacillus Calmette-Guerin (BCG) or chemotherapy are instilled into bladder with a catheter and held for 1-2 hours
- Usually started 2-6 weeks after TURBT
- Indications for intravesical therapy:
 - NMIBC with high risk of recurrence
 - NMIBC with high risk of progression
 - Carcinoma in situ
 - Residual tumor (rare indication for small volume tumors, TURBT almost always preferred).

INTRAVESICAL IMMUNOTHERAPEUTIC AGENTS



| Drug | Side-effects |
|------|--|
| BCG | Inflammatory cystitis (most have mild cystitis) Severe BCG cystitis (2-5%) Flu-like symptoms (10-15%) Fever (5%) Granulomatous prostatitis (1%) Sepsis (0.5%) |



If you really shouldn't have anesthesia, let's put some chemotherapy in there and see if we can slow down the cancer because we don't want to put you under anesthesia if it's very risky for you.

INTRAVESICAL IMMUNOTHERAPEUTIC AGENTS

BCAN
Bladder Cancer Advocacy Network

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the bladder or the kidneys or the prostate happens around 1% of the time. Fever can happen. Usually, it's low grade, somewhere between 5 and 10% of the time, along with these flu-like symptoms, some fatigue. Very high fevers are concerning though. If you have a fever over 101, 101.5, you really need to talk to your doctor because there is a small chance you either have an actual bladder infection from us putting a catheter in or, more rarely, an infection from the tuberculosis.

The chemotherapies can be lumped into a variety of different ways by which they work, but they mostly just cause some irritation in about 15 to 20% of patients. Similar to BCG, from the irritative standpoint, feeling like you have to go to the bathroom a lot or some discomfort or some urgency. Everything else, like myelosuppression, which is lowering your white blood cell count or other toxicity are very rare. They happen less than 1% of the time because these treatments should not be given if there's concern of perforation of the bladder or if you're not healed from your resection. Usually, if you wait two to three weeks and the bladder is healed, you don't absorb it and you don't get these systemic side effects like you would from IV chemotherapy.

The main side effects of BCG fall in line with how it works. BCG tricks your immune system to coming into the bladder. A lot of people have symptoms similar to what a bladder infection might be. You can have irritative symptoms, so you might feel like you have to go to the bathroom a lot. You might have some urgency, occasionally some pains, sometimes some bleeding.

Severe reactions are uncommon, so getting an actual tuberculosis infection of

INTRAVESICAL CHEMOTHERAPEUTIC AGENTS

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| Drug | Dose | Volume | Mechanism of action | Side-effects |
|--|--------------------------|-------------------------|---|---|
| Anthracyclines <i>Doxorubicin</i> <i>Epirubicin</i> <i>Vinorelbine</i> | 50 mg 50 mg 800 mg | 50 mL 50 mL 75 mL | Cross-links DNA/RNA Inhibits topoisomerase II | Chemical Cystitis (15-20%) Severe (3-5%) Cardiotoxicity (<1%) Myelotoxicity (<1%) |
| Antitumor antibiotics <i>Mitomycin C</i> | 40 mg | 20 mL | Cross-links DNA | Chemical Cystitis (15-20%) Severe (3-5%) Myelotoxicity (<1%) Skin Desquamation (if spillage onto skin) |
| Antimetabolites <i>Gemcitabine</i> | 2 g | 100 mL | Pyrimidine analog (fake nucleotide) G1/S cell cycle arrest | -Chemical Cystitis (5-10%) -Myelosuppression (<1%) |

ADJUVANT INTRAVESICAL THERAPY



- The standard induction course is the same for immunotherapies and chemotherapies
- Clinical trials have demonstrated benefit for maintenance therapy for both Mitomycin C and BCG.
- The most common maintenance schedule for BCG is the Lamm/SWOG regimen (triplets of BCG given at 3, 6, 12, 18, 24, 30 and 36 months).
- The most common maintenance schedule for chemotherapy is once monthly for 1-3 years.

Typically, we give the same number of treatments when we do induction, which is the initial treatment, a six-weekly treatment. Our clinical trials have demonstrated that there's a benefit from maintenance therapy, and so there's a variety of different maintenance schedules for BCG. You usually give three weeks of BCG at three months, six months, and then six months intervals. Some people do it for two years. Some people do it for three years. Some people even do it for one year.

As far as chemotherapy, it's usually given monthly for one to three years, and that again varies by what your risk is and how often you're recurring and things like that.

Overall, the response rate for BCG is better than chemotherapy, which is why it's typically used for high grade disease. It's about a 60% overall response for BCG and about 30 to 40% response for chemotherapy. There is, for high risk patients, superiority for a full dose of BCG. Sometimes, we'll lower the dose of BCG in patients who aren't tolerating it well, but three years was shown to be better than one year. Nobody really looked at two years specifically.

EFFICACY



- Overall 60% response to BCG and 30-40% for chemotherapy
- A large clinical trial recently demonstrated the superiority of 3 years of full dose BCG over reduced doses in high risk patients .
- BCG induction with maintenance has been shown to be better than Epirubicin and Mitomycin C in high risk patients.
 - This includes not only reducing recurrences, but also reducing the risk of progression to metastases and death.

We know that, if you give BCG and do maintenance, it's better than chemotherapy for high risk patients. It's the main treatment that has reduced the risk for progression. So for cancer becoming muscle invasive, it's our preferred route for patients who can tolerate it if they have high risk disease.

Dr. Yair Lotan: For intermediate risk patients, remember, these are patients primarily with low grade disease, but with multiple or recurrent cancer, BCG and chemotherapy are fairly similar in efficacy. Definitely, you want to use BCG as a first line for carcinoma in situ because it works much better than chemotherapy.

There is a problem though. Some tumors don't respond well to BCG. You want to give at least six months of treatment typically to know if BCG is going to work. Sometimes, it takes the

immune system a little bit longer to completely benefit or respond to these cancers. However, if after six months and you have high risk disease, even if you have not progressed, we'll typically talk to you about the primary way to cure you, which is to take out your bladder.

Now, this is even if you haven't progressed because we want to really take the bladder out before you progress or, God forbid, spread because then the chance of cure goes down dramatically.

There are other intravesical chemotherapies that are used sometimes. Valrubicin is one type of chemotherapy that is approved by the FDA, but, long term, it only works in one out of 10 patients. That's why we have a lot of clinical trials that we're trying to test other agents to see if they have a better response and we can keep your bladder in. There is about six or seven different clinical trials either using different types of chemotherapy or combination therapies. Some of them are using different virus conjugates where you actually use the virus that's not going to attack the body, but to insert DNA sequences that will make you make things that will either stimulate the immune system or possibly kill the cancer in a targeted way. None of them have conclusively shown a benefit yet. There are a variety of trials in different stages that are hoping to get approval from the FDA over the next three to five years, but at this time, at a lot of academic centers we usually have one or two of these trials open. Some of them are even using checkpoint inhibitors with the hope that we'll find some ways of preserving the bladder even though, right now, I'd have to say, the first and best option from a cancer standpoint is to take out the bladder.

The quality of life issues are lower in patients who and whom we take out the bladder, and that's a discussion that really needs to be held with each patient and the urologist when they get to that point.

EFFICACY



- For intermediate risk patients, BCG and chemotherapy are similar in efficacy.
- BCG should be considered first line therapy for CIS since the response rate is double that of chemotherapy.
- For patients who do not respond to BCG after 6 months of therapy options include:
 - Cystectomy
 - Intravesical chemotherapy (Valrubicin approved with 10% long term response)
 - Clinical trial

