



Jonathan Wright: So with that, we'll move on to our third case. This is a 64-year-old woman who also presented with hematuria, treated for UTI for a bit, but didn't get any better. Ultimately, a CT scan, which showed a two centimeter bladder mass, a little bit smaller than an inch. No evidence of any extension beyond the bladder, no enlarged lymph nodes. The kidney was not blocked off as it was in the last case. The urologist was able to completely resect all of the two centimeter tumor. Pathology came back as invading into the muscle wall. So a T2 urothelial cell carcinoma. There was no carcinoma in situ present from other spots of the bladder.

Otherwise, a healthy woman, I think importantly, no bothersome urinary symptoms whatsoever. So here is a person with a relatively small solitary mass and it's been resected and comes to us. What are the different treatment options, Dr Liao?

Jay Liao: Yeah, so this is a patient that's fortunately healthy enough for a variety of options. Obviously, the very standard option would be surgical management with a radical cystectomy like we talked about with the last case. As Dr. Grivas went through those improvement and outcomes with adding chemotherapy upfront before cystectomy. But this is the patient actually that raises the question whether there's a role for trying to preserve the bladder with chemo radiation. So I'll go through a little bit of kind of the background for that.

Case 3

64-year-old woman with blood in the urine (hematuria)

- No obvious urinary tract infection and hematuria persisted
- CT scan showed 2-cm bladder mass
 - No evidence of tumor extension beyond the bladder
 - No enlarged lymph nodes
 - No blockage of the kidneys (no hydronephrosis)
- Complete visual TURBT (resection) shows **T2** urothelial cell carcinoma (into the muscle); no CIS present
- Otherwise healthy
- She has essentially no bothersome urinary symptoms



Management of Muscle Invasive T2 disease

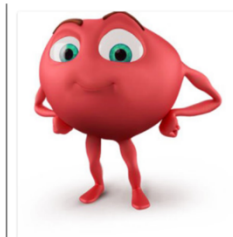
- **Candidate for Surgery**
 - Radical Cystectomy
 - Neoadjuvant Chemotherapy followed by Cystectomy
 - Chemoradiation for Bladder Preservation
- Clinical trials

Chemoradiation for Bladder Preservation



• Can the bladder be preserved and cancer treated effectively with nonsurgical therapy?

- Pioneered by MGH, University of Paris, University of Erlangen (Germany)
- 1980s: Studies in Paris looking at preoperative chemoradiation before surgery showed a number of patients with pathologic complete responses
- 1990s: German and RTOG/MGH experience showed encouraging results with Radiation therapy and concurrent Cisplatin based chemotherapy after TURBT
- Not as widely used in the U.S. compared to internationally
- Available at specialized centers with expertise in this approach

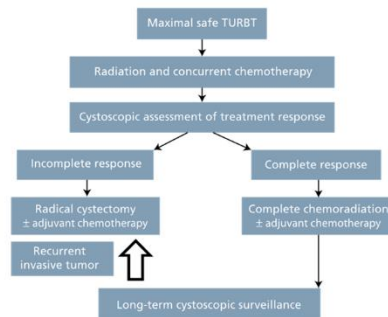


So can the bladder be preserved safely and can we also treat the cancer effectively at the same time? So this is a strategy that's been looked at across many types of cancers and trying to preserve organs basically. It's used in head and neck cancers, may be used in anal cancer. In bladder cancer this was pioneered by a group at the Harvard Hospital, Massachusetts General Hospital, as well as groups in Europe from Paris and Germany. What they found is, they basically stumbled on it, like many medical discoveries and they were looking at patients who are actually undergoing surgery, but

before surgery they had chemo radiation. They were surprised that there were a number of patients that actually had a complete response by the time the bladder was removed.

Jay Liao: So this led to investigation of, "well, maybe we could actually use chemo radiation as the primary treatment, in lieu of surgery." So this led to work both in a European groups as well as from cooperative groups in the US and Harvard Group, looking at this in a careful fashion. Overall, this has been less widely used in the United States compared to internationally where it's done much more often, but in specialized centers in the US and tertiary care centers with a little bit larger volume of patients with bladder cancer, and with groups that had expertise in this approach it's something that has been used and can be successful.

Chemoradiation for Bladder Preservation



Now this is the overall lay of the land just briefly with how we approach bladder preservation. So the role of the surgeon is still important here and that successful outcomes with bladder preservation are tied to actually be able to clear out the tumor to begin with, as maximally as possible by doing a maximal scraping or TURBT procedure. Following that patients undergo concurrent chemo radiation. So radiation is a daily process over weeks of therapy, generally over about seven weeks, but it's a split course. We're about two thirds of the way through the treatment. We do a repeat assessment, so patients go through about five weeks of radiation and chemotherapy, often given weekly.

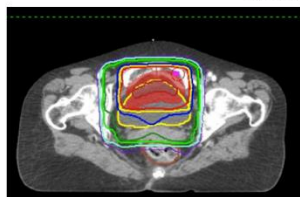
Then at that point we take a break and for about two or three weeks or so, there's a reassessment of where we do repeat cystoscopy to see if there's a response. So if there's no residual tumor at that point, we typically take a biopsy, then patients go on to complete what we call consolidative or some additional chemotherapy and radiation for about two weeks, two and a half weeks. If there's persistent cancer then our impression is that this is probably not the best strategy to continue with. So the patient be best served with a cystectomy at that point. So that gives us a little bit of an early look into whether the treatment's effective.

Importantly, after we get done with the treatment, if a patient does go through chemo radiation, it's important to have very careful cystoscopy surveillance because we want to catch if there's any persistent or any recurrent cancer to still give us outcome for dealing with recurrence at early point.

In brief, these are about the outcomes that we've seen with bladder preservation across numerous studies. The overall response rate at the end of treatment is on the range of about 75% to 80% as far as

Chemoradiation for Bladder Preservation: Outcomes

- Complete response rate: 60-90% (average 75-80%)
- ~20-25% may have residual tumor post-treatment
- ~20-30% may develop subsequent bladder recurrence
- Close long term surveillance after treatment is important
- Recurrence may be either non-muscle invasive or muscle invasive
- About 10-30% of pts eventually undergo salvage cystectomy
- 70-80% of survivors have intact bladder



the pathologic response with the treatment. This does mean that there's about a 20% to 25% chance that there could be residual tumor after the treatment, which would be an indication for doing a cystectomy, and some patients may have a complete response later on down the road, develop something that comes back in the bladder. So this is a testament to how important is to continue with close surveillance and why the involvement of the urologist is still really key here, even though we're treating the patient with primary chemo radiation.

Some recurrences are superficial recurrences where you may not have to remove the bladder. Some may be muscle invasive where we would have a discussion on whether to do a salvage cystectomy. The rates vary across different experiences, but somewhere around the order about 10% to 30%, there may be a chance of still needing bladder removed in the long-term. So it depends a little bit on how carefully you select the patients. In our experience has been on the lower end of that and many contemporary series hover around 10% to 15% chance of needing bladder removed in the long-term. So it does mean that a large proportion of patients when carefully selected have success with having an intact bladder.

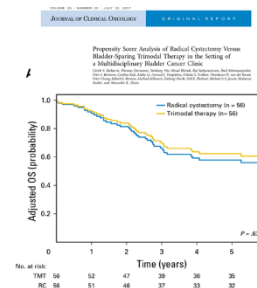
In an ideal world, we'd have a head to head comparison. But randomized trials and head to head studies are difficult to complete, especially like this. So it's hard to say how these measure up, at least available data that's tried to look at this retrospectively suggests that the outcomes may be similar when you look at similar stage patients. This was just one careful analysis by European group that took about a hundred match patients, 50 that had chemo radiation and 50 that had surgical management with similar characteristics as far as the stage and appearance of the cancer looking at the long-term survival outcomes. As you can see from the lines there, they were pretty much overlying suggesting that you may be able to achieve very similar results with this strategy.

Surgery versus Chemoradiation

- Difficult to compare due to pools of patients being different (age, stages, prognostic factors)
- 5 yr Overall survival rates of contemporary surgical series and bladder preservation approaches appear similar

Table 4 Invasive Bladder Cancer -- Survival Outcomes in Contemporary Series

Series	Stages	Number	Overall Survival	
			5 yr (%)	10 yr (%)
Cystectomy	U.S.C. 7 (2003)	653	46	32
	M.S.R.G.C. 7 (2003)	181	36	27
Bladder bladder preservation	Elwert 7 (2005)	329	45	29
	M.G.J.A. 7 (2003)	180	54	36
	B.T.C.C. 7 (1998)	123	46	—



So, one important key is that you have to select patients carefully for this approach. So, the ideal candidate that is a patient that might have good success with having good response to treatment and saving their bladders, one that has a small tumor that's in only one location or unifocal that's able to be cleared maximally by the urologist with a TURBT beforehand. No spreads, any lymph nodes, and ideally just in a single location without any evidence so what's called CIS, or precancerous change that would increase their risk of having a recurrence in the bladder down the road.

Chemoradiation for Bladder Preservation

> **Careful Patient Selection is Key**

> **Ideal candidate**

- Unifocal & small tumor < 5 cm
- Maximal/optimal TURBT possible (cT2)
- Node negative
- No extensive CIS or predominant variant histology
- No hydronephrosis
- Good bladder function
- Able to follow up for close surveillance

- *Only a subset of patients are optimal candidates*

Apparently in this case, which is in contrast to the prior case, we discuss no evidence of any kidney blockage or hydronephrosis is also an important factor. We try to just suggest patients that with considering the rest of their health and their baseline function have good bladder function to begin with so that we're actually providing meaningful improvement in their quality of life in the long-term. So it turns out only a subset of patients are really good candidates for bladder preservation. But this is a case where I think with a small tumor that's solitary, that's easy to be cleared with the TURBT and with no hydronephrosis. This would be a patient that I would be discussing in BCMC with the merits, and pros and cons of chemo radiation.

Jonathan Wright: Yeah. And this is one, where we're certain we're presenting to the patient a choice where there are two good options for consideration. One of the points that we have to have in the discussion is if they are in that 10% to 30% that need to have a cystectomy down the road, it can be a

Cystectomy Salvage for Recurrence after Chemoradiation



- No continent diversion
- Tissue healing complications more common
 - Wound issues
 - Scarring where bowels and urine are sewn together
 - Higher re-operative rate

harder operation. We do know that there are radiation does cause some scarring, so there can be more issues where we sew the ureters into the bowel, there can be cases where the bowels are sewn together. They're still a very manageable and we certainly do these operations. But it is important to have these discussions so the patient can weigh the different pros and cons.

We typically will not offer a neobladder in these settings because of the prior radiation

and the scarring effects from it, but certainly great patient for us to consider offering them different options. And certainly having BCMC as Dr. Liao said at the beginning, we have increased the number of patients who have been offered and selected bladder preservation with good outcomes. But I'll reinforce again his comment that we do this for the appropriately selected patients. So patient selection is key in this scenario. But again, even in this patient, there can be options for clinical trials as well.

Jay Liao: So one exciting thing that we're involved in that actually, attribute and recognize Dr. Wright's leadership enthusiasm and this is a study of trying to improve radiation targeting. So we're working with a company that manufacturers this gel material that actually can be used as a marker and imaging

markers, so it's called Trace-IT. So, we have a small pilot study, run by one of my colleagues, Dr. Zaing, that's looking at a temporary dissolvable marker to help to basically paint and localize where the tumor location is. So, this is done at the time that the tumor is removed or TURBT during the time of the endoscopy.

Basically, we placed these tiny gel markers along the borders of where the tumor was removed, and we can use this for radiation targeting. So we have an ongoing clinical trial that's open at the UW, SCCA looking at this. Just a few images here to illustrate how this works. Basically, cystoscopically the tumor is removed. This initial picture towards the upper left shows before the removal of the tumor on a CT scan. So you can see the tumor all along the left side of the bladder there. To the right to that image shows our radiation treatment planning scan after the tumor has been removed and then markers were placed at the time of the TURBT procedure.

Then now we can see clearly almost like a bullseye of where the tumor was removed.

I don't know if you can appreciate there, but in the absence of those markers you'd actually be a little bit challenging to localize actually where that tumor is effectively so they could us greater confidence that we're hitting the target. Then now we have technology nowadays during the delivery of the radiation therapy to actually verify this in real time each day, just before treatment. There's a low-dose scan called the Cone Beam CT scan that's built into the treatment unit that actually allows us to see those markers then and then align the radiation, being so that we can target the tumor very precisely.

Petros Grivas: I think that this is an example of how we can have a team approach and to present two options to the patient, and at the same time through clinical trials, again, we can even move the field forward. So Dr. Liao did an excellent job outlining how we would do radiation of patient and usually we'll try to use chemotherapy together with radiation for those patients who can tolerate chemotherapy. Chemotherapy in that particular context, can be one of three different options. We can use the cisplatin alone, once every week or another drug called gemcitabine alone once every three weeks, or a combination of 5FU, a different chemotherapy drug with mitomycin.

So there are three different chemotherapy recipes or regimen that we use in conjunction concurrently with radiation if someone can tolerate chemotherapy. Sometimes patients may not be able to tolerate chemotherapy whatsoever. Other scenarios in that case may get radiation alone, but the preference is to get concurrent chemotherapy and radiation.

Trace-IT Study

Temporary Intravesical Fiducial Marker for Bladder Cancer Radiation - A Pilot Study

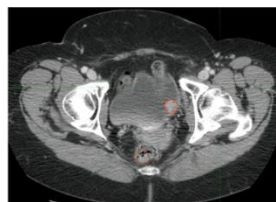


- Trace-IT™ hydrogel (*Augmentix*)
- Temporary dissolvable marker/gel placed around tumor
- Helps target the radiation therapy
- Ongoing clinical trial at UWMC & SCCA

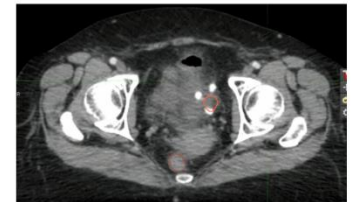


Goal: Improve radiotherapy planning and daily image guidance

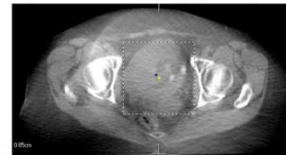
Initial pre-TURBT CT scan



Radiation treatment planning CT scan after TraceIT marker placement



Daily Cone beam CT imaging during Radiation



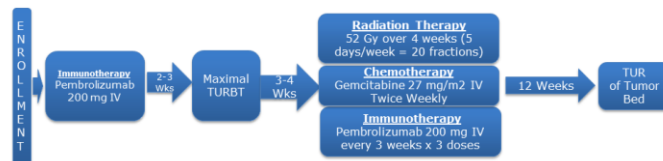
How can we improve the field? Can we move the field forward? One idea would be to combine chemotherapy, radiation and potentially immunotherapy. And this idea is being tested in clinical trials to see if the idea works. That trial by a Dr. Balar in NYU, is testing chemotherapy radiation and this anti-PD-1 checkpoint inhibitor together to see if this triplet effect can improve outcomes in patients with muscle invasive bladder cancer.

In a similar mood, we have a large clinical trial that is being launched in multiple parts of the United States. We call this SN SWOG/NRG 1806 trial. Very important trial with multiple of us being involved across the parts of the country. We try to answer the following question; Chemo radiation by itself or Chemo radiation plus immunotherapy? Whether again, the trifecta is better than the doublet. That's what we tried to do by randomizing patients to do either chemotherapy or radiation or that combination plus the anti PD-L1 agent Atezolizumab. This trial is looking at patients, who have even hydronephrosis, which is allowed only if it's only one side, and the kidney function is good enough. So it allows a little bit more patients compared to what traditionally we have used chemo radiation at. We're going to look at the percentage of patients who are alive without cancer, and they still have a bladder replaced.

Immunotherapy in Bladder Preservation

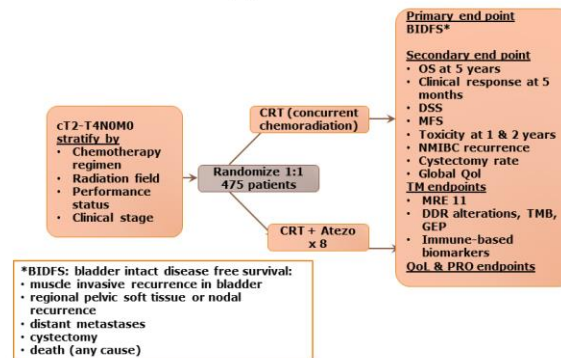


Phase II Trial of Pembrolizumab, Gemcitabine, Hypofractionated RT as Bladder Sparing Treatment for Localized MIBC



N= 54 (safety lead-in = 6)
 Primary Endpoint: BIDFS
 Participating Sites: 4 (Chicago, UNC, Michigan, MSKCC)
 PI: Arjun Balar (NYU); NCT02621151

Immunotherapy in Bladder Preservation



Plan to open at SCCA & UWMC in the next few months

PI: Parminder Singh

We have a lot of other metrics or end points that we're going to learn from over time. So we highly encourage multiple cancer centers in the country to think about that trial as we go forward. And we're opening this trial, we're in the process to open it at the University of Washington and Seattle Cancer Care Alliance in the next few weeks.

To conclude here, as an academic medical center, we did mention the word clinical trials and this last slide is just an overview of the management of bladder cancer that they made a few years ago. Is a 1000 feet view all the way from non muscle invasive bladder cancer, through muscle invasive bladder cancer, localized organ confined all the way to metastatic disease. And as you see in black is what the standard therapies with intravesical therapies. Neoadjuvant cisplatin based chemotherapy, cystectomy in pelvic

lymph node dissection or concurrent chemo radiation. You have a plethora of different clinical trials, but we have embedded in different pockets, spaces and settings of this disease to try to include opportunities for patients and try to improve the outcomes of those patients and try to move the field forward. How can we use novel agents like immunotherapy in different combinations and we do have multiple options available for patients.

So we have a balanced discussion for the right patient at the right time, what is the start of care therapy and what does a clinical trial option, and we have a discussion with the patient to decide the best fit for him or her. Overall, I think it's a wonderful experience and patients really enjoy this multidisciplinary approach. Thank you so much for having us.

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