Tri-Modality Therapy Background and Outcomes

Meet our Presenters

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Dr. Jason Efstathiou serves as the director of the Genital Urinary division of radiation oncology and Clinical Co-director of the Claire and John Bertucci Center for GU Cancers Multidisciplinary Clinic at Mass General Hospital. He holds a BS from Yale University and an MD from Harvard School of Medicine and a doctor of philosophy from Oxford University. He completed his residency training in the Harvard Radiation Oncology program. Dr. Efstathiou clinical practice focuses on the treatments of patients with bladder cancer and other neurologic cancers.
Bladder Preservation Therapy with Tri-Modality Therapy

Drs. Jason Efstathiou and Jim McKiernan

Jason Efstathiou: It's a pleasure to be on this webinar and really appreciate all the attendees for taking the time to discuss this topic of Tri-Modality Therapy for bladder cancer. I will start by discussing some issues surrounding radical cystectomy. The important point here is that radical cystectomy is a very good treatment for muscle invasive bladder cancer. Radical cystectomy is an excellent treatment for bladder cancer. And by no means is this presentation today meant to refute that point. It's just to show that there are options for patients. These options may not be for everybody but for those patients that are candidates for try-modality therapy it's an option worth discussing and knowing more about. There has been a paradigm shift in the world of oncology and organ preservation has become much more commonplace these days. Listed here are a number of cancers or organ conservation is commonplace. Such head and neck cancers, anal cancer, breast cancer, esophageal cancer and limb sarcomas. The question is “Why hasn't that become common with bladder cancer yet?” And we'll get into that a little bit in this talk. Again, one of the important things to note is that cystectomy is an excellent treatment and many patients do very well with a cystectomy, but it can be life altering.

This slide here shows some data from the Memorial Sloan Kettering Cancer Center which is a very high-volume center doing lots of radical cystectomies each year. And they honestly reported their complication rates following such a treatment, where 64% of patients had more than one complication and 13% of those were what we call high grade complications, grade three to five. A quarter of patients required readmission after a cystectomy for management of complications. And there was a non-negligible 90-day mortality rate associated with a cystectomy as well.

A Paradigm Shift: Organ conservation is commonplace in contemporary oncology

- Laryngeal carcinoma
- Anal carcinoma
- Breast carcinoma
- Esophageal carcinoma
- Limb sarcomas

Cystectomy is Life Altering

Morbidity of Radical Cystectomy (RC)

1142 RCs at MSKCC 1995-2005

- 64% More than 1 complication
- 13% Grade 3-5
- 26% Readmissions
- 2.7% 90 day mortality

No difference between open vs robotic assisted laparoscopic

Donat et al. Eur Urol 2009
Bachner et al. Eur Urol 2015

BCAN
The Memorial Sloan Kettering also ran a study trial that compared doing an open cystectomy or a robotic assisted cystectomy and the results from their studies suggested that there weren’t any major differences between those different types of approaches to doing the surgery. The question is how golden is the gold standard of cystectomy, given that there is some peri-operative morbidity associated with it. In addition, there are some other potential long-term issues. Number one, recurrence rates in the pelvis after a cystectomy are not necessarily low and late complications are not low. In this next slide I highlight some studies that were run at the University of Pennsylvania and confirmed within a cooperative national cancer group, called SWOG, that showed that pelvic recurrence rates, recurrences within the pelvis, could be as high as 40% in some patients after a cystectomy.

Other studies have suggested that in the long term, many patients suffer from renal or kidney function deterioration over time with some patients progressing to very significant renal dysfunction over time. The other important point, and this is really important, is that cystectomy is not being performed in about 50% of patients who have muscle invasive bladder cancer in the United States. So the average age of a bladder cancer patient is in the early 70s or late 60s. So they fall right into this group here. And as you can see, 50% of patients in that group are not receiving a cystectomy nationally for muscle invasive bladder cancer. And the question is what treatment are they receiving? And I can tell you that that gap is not being filled by tri-modality therapy at this time. And so, there is really a huge unmet need and there’s a real opportunity for tri-modality therapy, chemo radiation, which we’ll get into shortly to fill that gap.
Jason Efstatthiou: Let’s discuss tri-modality therapy a little bit further. What is it? Well, I think the first important thing is to recognize that it’s very much still a surgical approach although it is not radical cystectomy. A maximal complete transurethral resection of the bladder tumor, the TURBT, which can be done through a cystoscopic approach with a cystoscopy is critical, and those patients that have good complete receptions do better. Than that is followed by chemo radiation. And there are different ways of doing chemo radiation, so don’t get confused by this slide. But basically we go to a dose in terms of radiation dose that’s known to be potentially curative for bladder cancer. The urologist is represented by a U here showing that they remain very much a quarterback at this approach and are involved at different stages, including doing another cystoscopy and a re-biopsy of the area of the tumor following chemo radiation.

For patients who are doing well and have had a complete response after chemo radiation they go on to surveillance. And surveillance means lifelong cystoscopic surveillance. That in the first year or so, is done every three months and then the intervals will decrease to every six months and eventually yearly cystoscopies. If ever there is a recurrence of muscle invasive bladder cancer in the bladder, then a salvage cystectomy could be considered as a backup. So a tumor that has recurred and obviously wasn’t cured by the chemo radiation could still be cured by doing a cystectomy if needed later on.

What we know is that, again, that transurethral resection of the tumor and the salvage cystectomy are key to the success of tri-modality therapy. Here we’ve looked at the results from the Massachusetts General Hospital stratified by whether or not a complete to TURBT in red was achieved or not in black. And as you can see the outcomes are better if a complete transurethral resection is attainable prior to starting chemo radiation.
Here we see some long-term results of tri-modality therapy. For example, the five year survival rate from bladder cancer approaches 75% and this is in patients going back to the 1980s. This is very long term data. We would also argue that our data these days in the contemporary era are even better. So a patient with a T2 muscle invasive bladder cancer could expect five year survival rates of bladder cancer approaching 75% and 10 year rates on the order of about 66%.

Let's look at the outcomes of tri-modality therapy a little bit closer. Here our results shown in the contemporary era. And what do I mean by that? I mean patients treated since 2005. Basically the last decade or so. How are those patients doing? Well, the five year rate of surviving bladder cancer is now approaching about 85%. So I think our treatment has gotten better, our ability to select patients that would do well with this has gotten better. Radiation has gotten better, the chemotherapy has gotten better, the emphasizing of complete transurethral resection has gotten better and with that we're seeing some very promising results with this approach.

In addition, the need for a cystectomy due to a recurrence of the tumor in the future has gone way down. Back in the 80s, it was almost as high as 40%. Nowadays, it’s more like 15%. And if we look at other studies as well, and other series, I think a fair number to provide is 10 to 15% of patients may require a cystectomy following chemo radiation due to a recurrence. So what's the flip side of that? Well, about 85% of patients who've gone through tri-modality therapy these days will retain their native bladder in the long term.
Jason Efstathiou: Some folks ask “Well, what if the bladder cancer was it was a urothelial carcinoma?” which is the gotten variety most common form of bladder. But what if it has a little bit of squamous differentiation, or some other pathologic features like that? Can you still do tri-modality therapy? The results of this study suggests that yes, that survival rates appear to be pretty comparable, even if there is a mixed variant in the pathology.

How do these results of tr-modality therapy compare to the gold standard of radical cystectomy? Here is a large series of radical cystectomy showing survival rates in the long term. And what you see is that the 10-year rates of survival are about 60 to 66% survival from bladder cancer. And that applies to T2, T3 tumors and these are mostly the tumors we’re talking about when comparing to tri-modality therapy. So that’s why I’m focusing on this sort of orange and green line. And if you recall, the 10-year rate was 66%, with tri-modality therapy as well. So we think that these results are pretty comparable to radical cystectomy.

There are some studies though, in the literature that use large national databases that have gotten some press that suggest no cystectomy is better than tri-modality therapy in terms of survival in the long term. But we suggest caution in the interpretation of these types of studies. Because these types of studies that use large national databases like SEER or the National Cancer Database are fraught with issues. For example, they are not just looking at patients who were fit for surgery... they’re including a lot of patients that were unfit for surgery. So surgery was never going to be an option due to either age or medical comorbidities. Those patients were not excluded and so those are the patients that are certainly not getting surgery and may do worse in the longer term. In addition, studies like this have shown that inadequate radiation was delivered and so a lot of patients who were receiving either inadequate radiation or perhaps...
palliative radiation, so not radiation that was designed for cure, are again included in these kinds of studies. So, we just offer some caution for some of the studies that are out there.

If we want to look at the best available studies comparing tri-modality therapy to cystectomy, we can turn to a recent publication from the Toronto group. Where, they actually established a multi-disciplinary bladder cancer clinic where all patients saw the different specialties in the same setting. And were offered, for those that were candidates for cystectomy or tri-modality therapy they were offered either and some would choose one and others would choose the other. And then those patients were followed, and they were matched. So they had similar types of tumors, they had similar age, similar comorbidities, et cetera. And these patients were followed. As you can see here, tri-modality therapy in yellow and radical cystectomy in blue were not different in terms of survival. In the five-year disease specific survival, survival from bladder cancer again, was not statistically different between radical cystectomy and tri-modality therapy. And you'll recall these five year numbers were very similar to the MGH results of 75% that I had shown earlier. Again, in the contemporary era, our results may even be better as I had also shown earlier. But basically I think this is the best available data comparing tri-modality therapy to cystectomy in matched patients that were kind of equal to begin with.

**Jason Efstathiou:** Now an important part to the paradigm of tri-modality therapy. So why is it called tri-modality therapy? Well, one treatment is surgery. The transurethral resection, the TURBT, that's critical. And the potential 10 to 15% chance of savage cystectomy for backup. So that's one part of the tri-modality treatment. The second part is certainly the radiation which is treating the bladder, it's sort of replacing surgery. And then the third part of tri-modal is the chemotherapy that goes along with the radiation. It's called radio sensitizing chemotherapy. It's low dose chemotherapy that gives extra bang for the buck to the radiation. And that is an important component.

This study here that was run in the UK looked at doing radiation alone, so no chemotherapy, versus radiation plus chemotherapy in red and as you can see whatever line is on top means it is doing better, and the chemo radiation arm was better than the radiational arm. And here's another study run here in the United States in one of the cooperative
groups looking at different types of chemotherapy with radiation showing no big differences between those types of different forms of chemotherapy can be used with radiation and this next slide lists those options of good radio sensitizing drugs. Cisplatin is a classic standard, probably the one that has the most data over time. Paclitaxel, 5-FU and Mitomycin C, I'm going to show you that was the one that was used in this study here from the UK that I showed you. Gemcitabine, very low dose Gemcitabine. And then there's even these drugs called carbogen and nicotinamide which are hypoxia reducing drugs that tend to work well with radiation. Hypoxia is when there isn't sufficient oxygen in the tissue that you're treating. And these drugs reduce that and therefore make radiation more effective. The other important point here is there's lots of options for patients who are not candidates for cisplatin chemotherapy because cisplatin chemotherapy requires good renal function and a number of bladder cancer patients don't have good renal function. So, the good thing here is there's a lot of other good options that can be used in that type of scenario.