

Dr. Bivalacqua:

I'll now touch base upon muscle invasive bladder cancer so this is stage two or stage three disease. And this is where things change. We acknowledge that the standard of care for muscle invasive bladder cancer is no longer bladder preservation as it relates to putting medicine inside the bladder. This is where we start talking about giving systemic chemotherapy, followed by bladder removal or something called trimodal chemoradiation or TMT bladder preservation. Prior to any bladder preservation approach, which is chemoradiation, the patient should undergo a maximal TURBT so we can eradicate as much as possible any cancer. We know that response rates are much higher if we're able to do that. And this is identical to what we do when we do a re-staging exam prior to intravesical treatment so all the same rules apply.

Muscle invasive bladder cancer

Standard of care : neoadjuvant cisplatin-based chemotherapy (NAC) followed by radical cystectomy (RC) or trimodal chemoradiation (TMT)

Role of maximal TURBT

- All patients who are considering TMT must undergo a maximal/radical TURBT.
- Maximal TURBT (visually complete resection of the tumor) is the strongest predictor of both oncologic control and TMT success.
 - 20% increase in complete response and long-term bladder preservation in those receiving complete TURBT.

Efstathiou JA et al. Eur Urol 2012;61:705-11

Dr. Bivalacqua:

The Mass General is the group that Bill Shipley and Jason are really the people that have shown the most effectiveness of this. Clearly you have to be able to select patients for bladder preservation, and I'm happy to go over to that more in detail, but clearly there's evidence to support bladder preservation in select patients that actually are able to tolerate it. Nick James, who practices out of the UK showed in this really nice article, that the addition of chemotherapy to bladder preservation clearly improves overall survival and clearly prevents local regional spread and recurrence of invasive cancer. So radiotherapy alone is less effective and you need to combine this with chemotherapy.

TMT Criteria for Success

MGH Experience¹:

- But these are highly selective patients...
 - Visibly complete TURBT in 65%
 - No hydronephrosis in 83%
 - No CIS in 78%

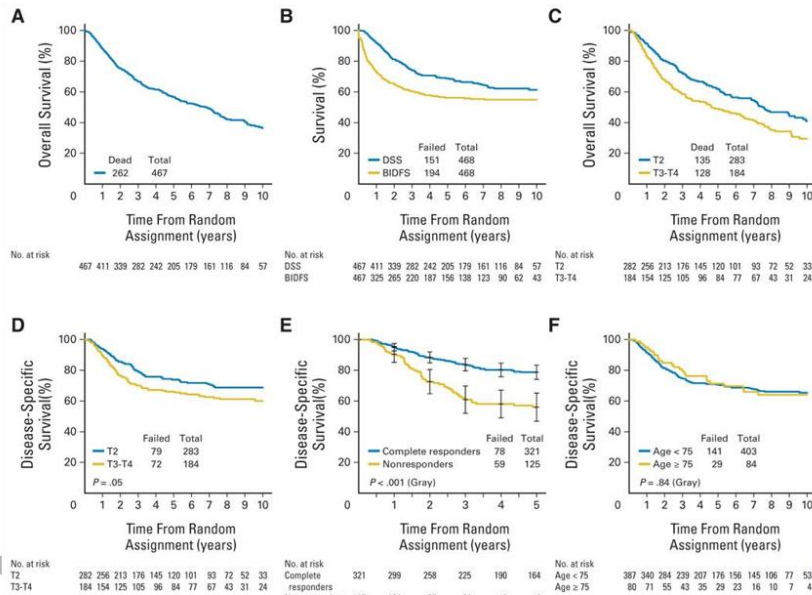
• Ideal patient²:

- Unifocal cT2M0N0 (no palpable tumor on exam)
- No hydronephrosis
- No CIS
- Good baseline urinary function
- No variant histology
- Ability to undergo maximal TURBT
- No involvement of prostatic stroma

These patients represent only 10-15% of MIBC³

¹Efstathiou et al. Eur Urol 2012.; ²Gakis et al. Eur Urol 2013.;
³Smith et al. BJU Int 2013.

RTOG protocols 8802, 8903, 9506, 9706, 9906, and 0233 – pooled analysis



Dr. Bivalacqua:

This is data that shows that from pooled analysis from RTOG trials, looking at bladder preservation. And I put this in here because you could see patients that had a nice maximal TUR received bladder chemoradiation therapy have really nice long-term survival. And we know that the disease specific survival is comparable to that of patients that underwent cystectomy with T2 disease. We know that chemoradiotherapy is more effective in patients with stage two disease versus stage three or four.

Long term outcomes. This is where it gets a little bit harder for patients to try to decide what they're going to do. We know that unfortunately, there are patients that do fail locally, where they develop recurrent cancers. Upwards of 50% of patients will recur with non-muscle invasive disease. We unfortunately know that about anywhere between 20 to 30% of patients will need their bladder removed or undergo a cystectomy. So this is something that has to be discussed with patients prior to considering.

Now what we also learned once again, through SWOG, this is Bart Grossman's trial, which showed that if a patient underwent systemic neoadjuvant chemotherapy, which is platinum based, if you received chemo prior to bladder removal, a

Long term outcomes following TMT

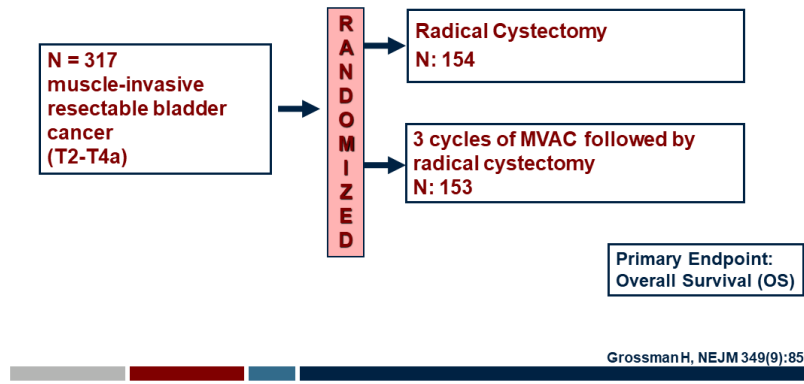
Table 2. Pooled Long-Term Outcomes

Outcome	No. of Patients	5 Years		No. of Patients at Risk	10 Years		No. of Patients at Risk
		Estimate (%)	95% CI		Estimate (%)	95% CI	
Local failure, any	212	43	39 to 48	148	48	43 to 53	39
Local failure, muscle invasive	56	13	10 to 17	191	14	10 to 17	52
Local failure, non-muscle invasive	156	31	27 to 36	162	36	32 to 41	44
Nodal recurrence	66	13	10 to 16	199	16	12 to 19	54
Distant metastases	153	31	27 to 36	188	35	30 to 39	53
Disease-specific survival	150	71	67 to 75	205	65	61 to 70	57
Bladder-intact disease-free survival	282	56	51 to 61	173	55	50 to 60	45
Overall survival	262	57	52 to 61	205	36	31 to 42	57

Mak RH et al. J. Clin. Oncol. 2014 Dec 1;32(34):3801-3809.

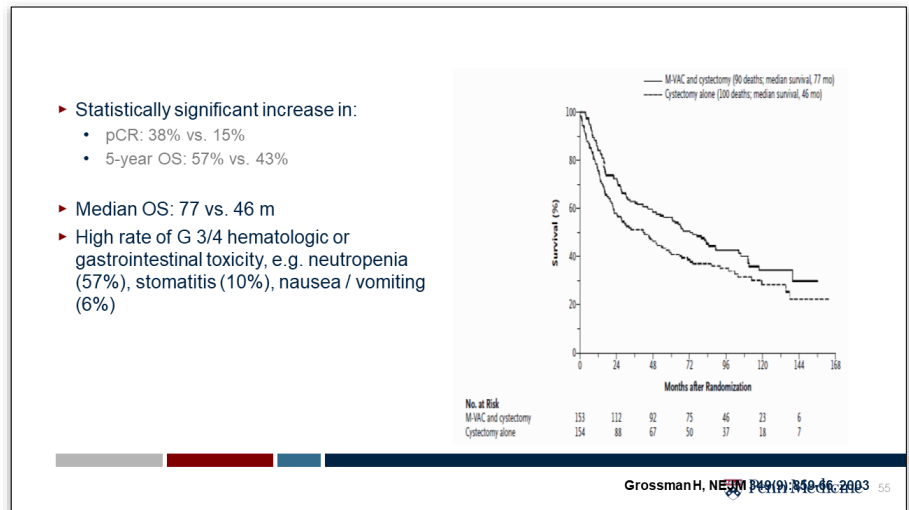
SWOG 8710

randomized controlled trial showed the following that you were able to prevent recurrence in cancer spread and you were able to have an improvement in overall survival in patients. So this has become standard of care prior to bladder removal.

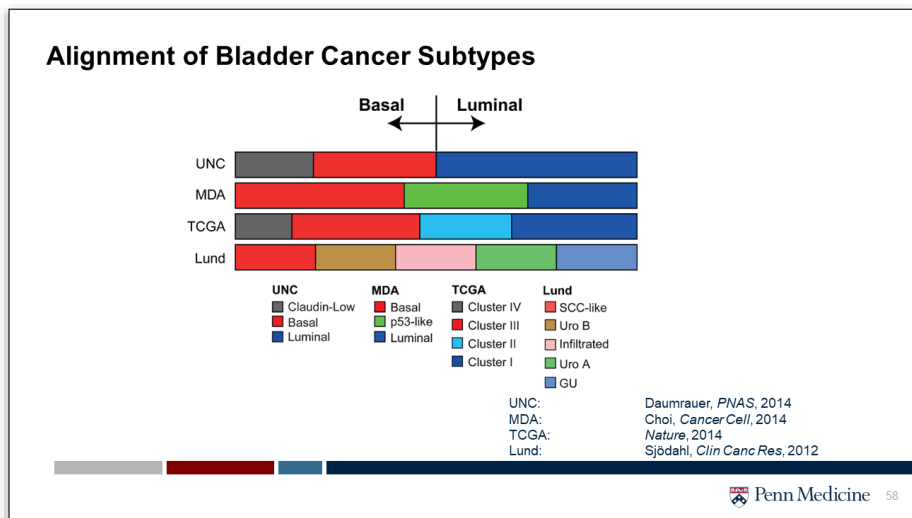


Dr. Bivalacqua:

Now, in my practice, everyone I refer for chemotherapy that is eligible. Not all patients are eligible. And what I mean by that is that they're not able to tolerate chemotherapy so we have to do a bladder removal in those that are not candidates for TMT. Also, we know that in the future, there are multiple studies that are now looking at things like immunotherapy in the neoadjuvant setting. This is the problem with neoadjuvant chemotherapy. We know that if you receive neoadjuvant chemotherapy, this is actually a Kaplan-Meier curve that looks at percent cancer specific survival. If you get chemo prior to bladder removal, and you have no evidence of cancer that is spread to lymph nodes or invasive cancer, you actually have a wonderful disease specific survival, upwards of 90%. If you are a non-responder where the chemo, where you still have significant disease in your bladder, your overall ability to survive is much less.



So in the field, what a lot of people have tried to figure out is, is there a molecular marker, biomarker? Is there a genomic test? Is there a mutation status that would predict response to chemo and be able to help guide our treatment options? This is a proposal of how we would do that. If a patient had a subtype directed therapy, if they had luminal cancer, they would get potentially upfront cystectomy. If they had a basal, you would get chemo. If you had a luminal infiltrated, you would get immunotherapy.



Dr. Bivalacqua:


Unfortunately, I'm here to say that we are not there yet and we do not have strong evidence that would say that this is now standard of care. This is something that we all are striving to do, but we unfortunately are not there just yet to be able to do that. So this was one of the questions that came up in there.

So in conclusion, I would say that TURBT and pathology evaluation provides diagnosis of stage and grade of bladder cancer, which is used to determine treatment


recommendations for both non-muscle invasive and muscle invasive disease. BCG and chemotherapy is used for intermediate and high risk disease. Excuse me. Options beyond BCG include combination chemo and new FDA approved agents are actually on the way. And remember, if you unfortunately have muscle invasive bladder cancer, we know that the utilization of new adjuvant chemo prior to radical cystectomy is now standard of care, as well as bladder preservation approach, which combined chemoradiotherapy with TURBT. That is my last slide. I thank you very much. I'm going to grab some water and I'm happy to answer any questions. Thank you.

Subtypes-Directed Therapy

	Outcome with Cystectomy Alone	Outcome Chemo + Cystectomy	Response to Immunotherapy
Luminal	Best	Same as RC	Intermediate
Luminal infiltrated	Poor	Poor	Best
Basal	Poor	Best	Worst
Claudin-low	Poor	Intermediate	Intermediate

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Concluding remarks...

- ▶ TURBT and pathology evaluation provides diagnosis of stage and grade of bladder cancer which is used to determine treatment recommendations for NMIBC and MIBC.
 - ▶ Intravesical BCG and chemotherapy used for IR and HR NMIBC. New options beyond BCG including combination intravesical chemotherapy and new FDA approved agents represent best salvage therapies.
 - ▶ Neoadjuvant chemotherapy prior to radical cystectomy is standard of care as well as bladder preservation (chemoradiotherapy + TURBT).
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