Introduction

According to Surveillance, Epidemiology, and End Results Program (SEER) estimates, there were over 74,000 new cases of bladder cancer and greater than 15,000 associated deaths in 2014, which remains largely unchanged over the last 25 years (1). Of these patients, 30% have muscle invasive bladder cancer (MIBC) at presentation and another 10% will progress from non-muscle invasive tumors. Radical cystectomy (RC) is the established standard of care for organ-confined tumors and has proven efficacy with extended follow-up cohorts reporting 5-year disease free survival from 68-85% (2-4). However, patient survival diminishes with increasingly advanced primary tumors, with a steep drop off once the cancer becomes non-organ confined or metastatic. Since currently available salvage therapies have very low rates of durable responses, with the notable exception of the recently FDA approved MPDL3280A (5), efforts to increase the success of definitive treatment have led to the utilization of perioperative chemotherapy.

Neoadjuvant chemotherapy (NC) has emerged as the preferred modality of delivering systemic therapy to non-metastatic MIBC patients planning to undergo RC. Based on evidence that will be enumerated below, NC provides a statistically significant survival benefit to patients. The benefit, however, is modest and the toxicities are prevalent, which has resulted in infrequent use of NC because of the perceived high risk (HR) and low benefit of the therapy (6). In this environment, there is an increasing demand to develop strategies that inform medical decision making to ensure those who require more aggressive therapies receive them. This article will review current and ongoing research on risk-stratified methods of identifying ideal candidates for NC.

The Case for NC

The question of perioperative chemotherapy was first addressed in the adjuvant setting with patients with extravesical disease or lymph node metastasis. A prospective trial from Skinner et al., demonstrated that adjuvant chemotherapy (AC) could improve relapse free survival in...
cystectomy patients from 46% to 70% (7). While there were subsequent randomized trials that confirmed this finding (8,9), there were still others with negative findings (10–12). Ruggeri et al. performed a pooled analysis of published phase III trials (n=5) and found that both overall survival (OS) and disease-free survival (DFS) were improved by the use of AC [response rate (RR) 0.74 and 0.65, respectively, P≤0.001] (13). Vale et al. further expanded on these results by performing a meta-analysis of the individual patient data from these randomized controlled trials (n=6) and corroborated the previous findings, showing a 25% risk reduction for OS, albeit with limited power (14). The recently published results of EORTC 30994, which compared immediate to salvage chemotherapy, appear to challenge the previous conclusions, as they did not demonstrate an OS advantage (47% vs. 57% mortality, respectively, P=0.13), suggesting that timing is not important for survival (15). However, the authors note that despite limited power for OS outcomes, progression free survival (PFS) was significantly improved (OR 0.54 for immediate), and there may be subgroups that can benefit from immediate AC. These studies demonstrate the importance of multimodal therapy in improving survival outcomes for patients with a poor prognosis with surgery alone.

In nearly all of these trials, a significant portion of the study population did not receive the complete AC regimen, which contributed to the lack of survival advantage in some trials. The low AC completion rate is, in part, attributed to the well-known high morbidity of RC, with quoted complication rates as high as 64% (13% high grade complications) (16). Donat et al. further examined this concept in a comprehensive examination of complication profiles among RC patients, and concluded that up to 30% of patients would be unable to receive timely AC due to prolonged recuperation (17). Additionally, the toxicity of the AC regimen is known to be particularly severe (18,19), which is compounded with the recovering state of post-operative patients resulting in as few as 56% of patients getting complete therapy in contemporary series (20). These results suggest that administering chemotherapy prior to RC might be a more favorable strategy to ensure patients are able to receive a complete chemotherapy course within the perioperative period.

There are several potential advantages of using NC instead of AC. Whereas extended surgical recovery precludes many patients from receiving or completing AC, giving chemotherapy up front when patients are at their optimal performance status increases the chance they receive the full dose/course of NC. The possibility of a complete tumor response, with the associated dramatic increase in survival, is the most compelling argument for NC. Nodal downstaging is another desirable outcome since occult lymph node metastasis is seen in 30–40% of cases, most likely due to micrometastatic disease not visualized on routine radiologic imaging (21). Finally, the degree of tumor response to NC gives a measure of in vivo drug sensitivity, which may also provide information on prognosis and choice of adjuvant/salvage therapy.

**Evidence for NC**

Through numerous prospective clinical trials, it has been determined that the ideal regimen for bladder cancer includes cisplatinum, and that replacement with other platinum based agents was not sufficient (22,23). The combination of methotrexate, vinblastine, adriamycin and cisplatinum (MVAC), initially described by Sternberg et al., has been shown to be the most effective regimen for bladder cancer, with overall RR of 65–72% in the metastatic setting (24,25).

Millaen et al. designed one of the early trials examining whether NC was a viable treatment alternative by comparing NC plus AC to AC alone, using the MVAC regimen (26). Although they did not demonstrate a survival benefit in this study, subgroup analysis showed that those rendered pT0 derived significant benefit. Based on these results, the utility for NC became more evident in this patient population. In the landmark SWOG-8710 study, Grossman et al. demonstrated that NC utilizing MVAC increased median survival from 46 to 77 months, and enhanced pathologic downstaging, with pT0 seen in 15% and 38% of RC and NC + RC patients, respectively (27). Griffiths et al. reported that cisplatin, methotrexate and vinblastine (CMV) could also produce a 16% reduction of the risk of death, with long term follow-up (median 8 years) (28). The analysis of the two Nordic trials by Sherif et al., demonstrated that even when combined with preoperative radiotherapy, cisplatin based regimens yielded at 20% relative and an 8% absolute risk reduction in death (29). Schultz et al. defined the importance of pre and post NC tumor stage in predicting survival, and confirmed that NC improves outcomes in patients with tumor downstaging (30). In subsequent meta-analyses of NC trials, it was shown that an absolute 5–6.5% OS benefit is observed when using MVAC NC for MIBC (31,32). The efficacy of this regimen is, unfortunately, tempered by an unfavorable toxicity profile, with documented granulocytopenia (33% grade 4).
and gastrointestinal complications (17% grade 3-4) (27).

To mitigate these adverse effects, alternate regimens have been developed that retain the same efficacy of MVAC. Some centers have recently modified the standard 4 week cycle, to a 2-week cycle with granulocyte colony-stimulating factor (G-CSF) support, known as dose dense MVAC (ddMVAC) (33). Follow-up clinical trials in the neoadjuvant setting have demonstrated that ddMVAC results in effective RR (pT0 =26-38%), far less toxicity (0-10% grade 3-4) and more patients completing the full course (93-95% completion) (34,35). More popular is the combination of gemcitabine and cisplatinum (GC) which was shown by von der Maase et al. in a phase 3 study to have similar outcomes compared with MVAC, but with more tolerable toxicity (36). However, since the design of this trial was to establish superiority, not equivalence, the evidence does not strictly support the widespread use of GC as an alternative to MVAC. Zargar et al. recently published a multicenter retrospective study that compared GC to MVAC, with two important findings; GC was utilized in the majority of patients (64%) and no significant difference was seen in pathologic RR or OS (37). Regardless of the regimen used, NC has level 1 evidence to support its use (Table 1), which is reflected in published guidelines that recommend offering NC to MIBC patients who will be treated with RC (38,39).

### Are all MIBC patients equally responsive to NC?

There is a growing utilization of NC, with Zaid et al. reporting an increase from 7.6% to 20.9% over a 4-year period, but this still represents a minority of patients (40). The biggest factor behind the limited application of NC for RC candidates is the modest OS benefit observed in clinical trials, which is contrasted with notable toxicity and potential for delaying surgery in chemotherapy non-responders. Scrutinizing the data lends credence to this view and reveals that the survival advantage is largely seen in responders. Unfortunately, only 30% of patients achieve a complete response, and another 44% will have some degree of downstaging. This leaves the majority of patients over treated if NC was offered to all candidates. Additionally, when looking at the RC only arm, there is a 15% pT0 RR demonstrating that a complete TURBT may be sufficient to render these patients downstaged and likely accounts for half of the downstaging seen with NC (27). The survival outcomes of these patients are similar to those of NC pT0

| Study | Treatment type | Year | Sample size | Regimen | OS | DSS | RR |
|-------|----------------|------|-------------|---------|----|-----|----|
| Skinner et al. (7) | Observation vs. AC | 1991 | 91 | Cisplatin, doxorubicin, cyclophosphamide | 2.4 vs. 4.3 yrs | – | – |
| Martinez-Piñeiro et al. (22) | NC | 1995 | 122 | Cisplatin | 36% | – | 34% |
| von der Maase et al. (36) | Salvage chemotherapy | 2000 | 405 | MVAC vs. GC | 38% vs. 37% | – | 46% vs. 49% |
| Millikan et al. (26) | AC vs. NC + AC | 2001 | 140 | MVAC | 4 yrs | – | 40% |
| Grossman et al. (27) | RC vs. NC + RC | 2003 | 307 | MVAC | 35% vs. 41% | – | 38% |
| Sherif et al. (29) | XRT + RC vs. NC + XRT + RC | 2004 | 620 | Cisplatin, doxorubicin or cisplatin, methotrexate | 48% vs. 56% | – | 80% |
| Griffiths et al. (28) | RC/XRT vs. NC + RC/XRT | 2011 | 976 | CMV | 30% vs. 36% | 54% vs. 59.7% | – |
| Pлимак et al. (34) | NC | 2014 | 40 | Dose dense MVAC | – | 87.5% | 53% [37-68] |
| Choueiri et al. (35) | NC | 2014 | 39 | Dose dense MVAC | – | 79.5% | 49% [38-61] |
| Sternberg et al. (15) | AC immediate vs. delayed | 2015 | 284 | GC, MVAC, or high dose MVAC | 54% vs. 48% | 61% vs. – | 57% |

OS, overall survival; DSS, disease specific survival; RR, response rate; AC, adjuvant chemotherapy; NC, neoadjuvant chemotherapy; MVAC, methotrexate + vinblastine + diaminycin + cisplatinum; GC, gemcitabine + cisplatin; XRT, radiation therapy; RC, radical cystectomy.
patients, 82% and 85% 5-year OS, respectively (41, 42). These results clearly point to the fact that only a certain subset of MIBC patients will respond favorably to cisplatin based NC.

To understand which patients most likely benefit from NC, Sonpavde et al. examined the patterns of survival and relapse from the SWOG-8710 study (43). Firstly, they observed that the RR was dependent on the baseline clinical stage, with cT2 patients downstaged 55% of the time, and cT3/4 patients 35% of the time. Similarly, the RR for pT0 was also stage dependent, 39% and 24% for cT2 and cT3/4, respectively. They also found that survival was dependent on the degree of response (median survival pT0 = 13.6 years, pT1/a/is = 10.6 years). Conversely, very poor outcomes were seen in patients who had no response or progression of disease (median survival of 3.7 years for pT2+). Paradoxically, when compared survival of non-responding cT2 and cT3/4 tumors (median survival of 1.8 and 5.1 years, respectively), the advanced clinical stage has a better prognosis. Overall, this report highlights that the baseline clinical stage is inversely related to the likelihood of response and that the final pathologic stage is prognostic of survival.

**Risk factors**

In order to selectively administer NC to the patients that will derive some benefit, researchers have tried to determine if there are preoperative factors that can be used to predict which patients will have the poorest outcomes. These can be roughly divided into those factors that represent locally advanced disease [palpable or fixed mass on examination under anesthesia (EUA)], cross-sectional imaging revealing signs of extravesical extension or local organ involvement, hydronephrosis) and those factors that predict regional/distant metastasis [lymphovascular invasion (LVI), and variant histology] (30, 44-50).

Locally advanced disease is challenging to accurately diagnose, but has a significant impact on outcomes. The utility of a good physical exam can never be underestimated, and the presence of a 3-dimensional palpable mass on bimanual EUA is consistent with a cT3b stage, and if that mass is fixed, cT4b (51). Cross-sectional imaging is important for local and distant staging in any malignancy, however computed tomography (CT) imaging has a limited efficacy in bladder cancer, plagued by poor accuracy (49-55%) and high interobserver variability (κ = 0.23-0.35) (52, 53). Dynamic magnetic resonance imaging (MRI) has proven itself to have moderate staging accuracy (62-63%), and good ability to distinguish organ confined from locally advanced disease (82-90%) with strong interobserver agreement (κ = 0.80-0.89) (54, 55). Hydronephrosis has been proven to be a surrogate for invasive disease for many years (46), with risk increasing from unilateral to bilateral involvement (90%≥ pT3 with bilateral). Bartsch et al. showed in their study that hydronephrosis was an independent predictor of recurrence free survival (χ² = 10.1, P = 0.0015) (56). In early trials with bladder sparing tri-modal therapy, it was quickly determined that patients with hydronephrosis had such an abysmal success rate, that it is now considered a standard exclusion criteria (57). Currently, the best predictive information on extravesical disease comes from a combination of physical exam and radiologic imaging.

Metastatic disease, either to the regional lymph nodes or to distant sites, portends the worst prognosis, and yet, in the absence of measurable disease, there are only a few options to help guide clinicians. LVI is the strongest pre-surgical predictor of poor outcomes, able to independently predict OS, disease specific survival (DSS), recurrence (local and distant) in pN0 patients (58, 59). There is data that suggests that the presence of LVI may predict failure of MVAC AC to improve outcomes in organ confined, node negative patients (60). Variant histology in bladder cancer includes many subtypes, but the variants that are of interest regarding early metastasis are micropapillary, small cell/neuroendocrine and plasmacytoid. Micropapillary is likely underreported due to interobserver variability both in academic institutions and community practice (61, 62), but it is universally accepted that invasive micropapillary disease is associated with a higher incidence of extravesical and metastatic disease, and poor OS (63, 64). While there is some data suggesting that NC may have efficacy in this group, due to small sample sizes, no definitive recommendation can be made (65). Small cell or neuroendocrine histology is another urothelial variant that has a grim prognosis. The largest series is from MD Anderson, with 172 patients in the cohort, with 50% of RC candidates receiving NC. NC has been shown to have a dramatic effect in this disease, with 62% downstaged to ≤ pT1 and a median OS improvement from 18.3 to 159.5 months (66). Plasmacytoid is a very rare and extremely aggressive variant of bladder cancer that has a predilection for peritoneal metastasis (67, 68). Dayyani et al. reported a series of 31 patients (median OS, 17.7 months) in whom 5 received NC, with 80% downstaging, but with early relapse and no demonstrable difference between upfront surgery (69). In total, these are the only significant

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 Recently, Culp et al. described the MD Anderson paradigm of classifying MIBC patients as low risk (LR) or HR based on these well-established factors, and correlated risk of upstaging and survival outcomes with RC alone (70). The classifiers of HR status are a palpable/fixed mass on EUA, radiologic evidence of cT3/4, the presence of hydronephrosis, LVI and variant histology. By analyzing their own series and using an external validation cohort, they found that LR patients had a 5-year OS and DSS of 64.8% and 82.7%, respectively, and 5-year OS and DSS for HR patients were dramatically worse at 47% and 68.2%.

The surprising finding is that the risk of upstaging in the LR cohort was 49.2%, but the group overall had reasonable outcomes. Looking at the HR category, those patients that were downstaged to LR on final pathologic staging (26.5%), had a 5-year OS and DSS of 85.1% and 91%. These same findings were corroborated by the external validation cohort, which had a much larger sample size. This schema of risk assignment gives NC to those patients at the highest risk of poor outcomes, while allowing LR patients to be promptly treated with RC, and avoid NC toxicities.

**Molecular classification of MIBC**

There has long been an effort to characterize bladder cancer using molecular markers that represent the underlying biologic processes driving the disease course. The prototypical molecular target in bladder cancer was p53, which was identified in the early 1990’s as being correlated with grade, stage and risk of tumor progression (71-73). A follow-up study was performed at Memorial Sloan Kettering using immunohistochemistry on patient samples from an NC MVAC trial, which revealed that nuclear accumulation of p53 was independently predictive of DSS, with a relative risk of 3.1 (74). Unfortunately, conflicting reports afterwards have led to an indefinite determination on whether p53 is truly a biomarker of survival (75). The robustness of the molecular findings was limited by the technology available at the time, and may account for the variable results generated by the different study groups.

With the advent of next generation sequencing (NGS) and high throughput microarrays coupled with bioinformatics techniques, genomics research has been able to make large leaps in the discovery and understanding of the mechanisms of oncogenesis. In early 2014, The Cancer Genome Atlas (TCGA) Research Network released the results of their whole exome sequencing and whole genome expression profiling analysis of MIBC (76). There were significant alterations in 32 somatic genes, including TP53, RB1, FGFR3, EGFR, PPARγ and many others. Unsupervised hierarchical clustering of the sequencing data yielded three intrinsic molecular subtypes; group A enriched with copy number alterations, group B mainly comprised of papillary histology and FGFR3 alterations, and group C enriched with TP53 and RB1 mutations. In addition to this the TCGA, in parallel with groups at MD Anderson Cancer Center and University of North Carolina, used similar clustering techniques to identify molecular subtypes based on with gene expression data (77,78). While there are important differences between the classification systems, in general, they were able to mirror the pattern seen in breast cancer, identifying basal and luminal subtypes that are enriched with gene sets that reflect the milieu of the different lineages. Damrauer et al. demonstrated that cluster K1 expressed high molecular weight keratins and CD44, which are seen in basal cells, and cluster K2 expresses low molecular weight keratins and uroplakins, both seen in urothelial umbrella cells. When correlating the subtypes with clinical outcomes, they observed that basal tumors had poorer survival compared with luminal tumors. Choi et al. identified a similar basal/luminal dichotomy, with basal enrichment of p63 and squamous differentiation and luminal tumors with PPARγ. Additionally, they identified a subset within the luminal subtype that was characterized as “p53-like” and displayed significant platinum chemoresistance, both in the clinical cohort and in subsequent cell line studies. In addition to setting a benchmark for comprehensive genomic analysis of bladder cancer, these groups have established a classification framework that researchers can continue to refine.

Using similar techniques, other groups have correlated genomic findings to clinical outcomes that may inform patient management. Turo et al. created a tissue microarray using samples from the primary tumor and metastatic lymph nodes in patients that were clinically node negative prior to RC (79). Examining FGFR3 specifically, the authors found that there was a high concordance between the specimens (OR 8.45), even when using multiple samples from each site to account for intratumoral heterogeneity. This suggests that FGFR3 protein expression in the primary tumor can be used to identify patients at a HR of occult lymph node metastasis, and candidates for NC. Groenendijk et al. used NGS methods to compare the mutational profile of complete responders and non-responders to NC (80). Their group found that ERBB2 activating mutations
were exclusively found in the responder cohort, with none present in the non-responders (P=0.003). ERCC2 mutations also appeared to be differentially expressed with 16% of responders and 6% of non-responders having the mutation, however this was not significant (P=0.27). Van Allen et al., however, performed whole exome sequencing on patients receiving cisplatin-based NC and demonstrated that ERCC2 mutations were enriched in responders (81). Further in vitro work demonstrated that ERCC2 deficient cell lines increase cisplatin sensitivity, and this effect is rescued with wildtype ERCC2, but not the mutant form found in the patient cohort. Font et al. analyzed gene expression in NC patients and found that high BRCA1 expression in pre-treated tumors predicted lower NC response (22% vs. 66%, P=0.01) and lower OS (HR 2.73, P=0.02) (82). Using molecular characteristics to identify patients with HR disease or to predict patients likely to respond to NC, the major contribution of these efforts is that this information is correlated to a meaningful difference in clinical behavior, demonstrating the importance of translational research.

Conclusions

If we could perfectly identify responders to NC, or if the toxicities were minimal, utilization rates would be much higher than they are now. Unfortunately, neither of those conditions is currently true. We now know that there are factors that we can use to stratify patients into high and LR. Even with a high incidence of upstaging amongst LR patients, it has been shown that their outcomes with RC alone are similar to patients that had no stage change. But this binary system is still a relatively unsophisticated way of guiding decision making. Knowing that we can identify patients who do well with surgery alone, we now need to identify which HR patients will respond well to cisplatin based NC, and those who need alternate treatments based on novel targets.

New molecular classifiers are being created to characterize tumors based on the underlying cancer biology, with important implications concerning progression and chemoresistance. This is certainly the direction that bladder cancer research needs to follow, in order to refine decision making to attain the goal of personalized medicine. Already several genomic classifiers have been developed, which have been designed for predicting DSS after cystectomy. The most recent, developed by Mitra et al., is a 15-gene classifier that predicts recurrence after RC without NC, with superior performance compared with currently available clinical predictors. In a more prospective fashion, the recently activated SWOG-NCI sponsored COXEN clinical trial (S1314) plans to compare GC and MVAC NC, and simultaneously collect tissue, blood and urine samples to process through the COXEN algorithm (83). The COXEN algorithm has already been able to develop and validate a multivariate gene expression model for survival in NC treated bladder cancer, using a combination of publicly available human microarray data sets and in vitro drug sensitivity testing using the NCI-60 cell line panel (84). In the current prospective trial, gene sequencing and expression profiling will be performed to analyze oncogenomics, expression patterns of coding and non-coding RNA, and pharmacogenomics. Instead of simply comparing two different NC regimens, this trial is unique in the fact that it will allow investigators to discover patterns of sensitivity/resistance and develop molecular signatures to guide decision making in multimodality cancer treatment. With the initiation of more trials like this, we will be able to test new therapeutic agents, and ideally be able to predict the right drug for the right patient at the right time.

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Footnote

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