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Modeling Cost-Effectiveness of a Biomarker-Based Approach to Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer

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Abstract

Objectives: To model the cost-effectiveness (CE) of a biomarker-based approach to select patients for neoadjuvant chemotherapy (NAC) prior to radical cystectomy (RC) in muscle-invasive bladder cancer (MIBC).

Materials and Methods: We obtained most recently clinical studies on locally-advanced bladder cancer treated by RC, including stage distributions, overall survival (OS) estimates, associated costs, and utilization/response to NAC. Additionally, we estimated the putative efficacy of 3 biomarkers to select patients for NAC: DNA repair gene panel [*ATM*, *RBI*, and *FANCC*], *ERCC2*, and RNA subtypes. A decision analysis model was developed to evaluate the CE of biomarker-based approaches to select patients with MIBC for NAC. Comparison of CE included RC alone, unselected NAC plus RC, and NAC based on the 3 aforementioned biomarkers.

Results: The DNA repair gene panel-based approach to NAC was the most CE strategy (mean OS of 3.14 years, \$31,482/life year). Under this approach, 38% would undergo NAC, approximately twice the number of patients who are currently receiving NAC for MIBC. Such an approach would improve mean OS by 5.2 months, 1.6 months, and 4.4 months compared to RC alone, a hypothetical scenario where all patients received NAC, and compared to current estimates of NAC utilization, respectively.

Conclusions: A biomarker-based strategy to identify MIBC patients who should undergo NAC was more cost-effective than unselected use of NAC or RC alone. As further data becomes available, such a model may serve as a basis for incorporating biomarkers into clinical decision making.

Keywords

bladder cancer; biomarker; cost; neoadjuvant chemotherapy; response

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INTRODUCTION

Despite level 1 evidence,(1–3) adoption of neoadjuvant chemotherapy (NAC) prior to radical cystectomy (RC) in patients with muscle-invasive bladder cancer (MIBC) has been slow and rates of utilization hover between 20-30% nationwide.(4) Randomized trials evaluating NAC in patients with T2-T4aN0M0 disease indicate an overall survival (OS) benefit with hazard ratio (HR) of 0.87 and absolute survival benefit of 5-10%.(2, 3) Beyond potential toxicity concerns, lack of utilization is related to a perceived relatively low benefit and concern that many patients with organ-confined disease do not need additional treatment.

A predictive biomarker for response to NAC could avoid chemotherapy in those unlikely to respond and thereby expedite surgery and reduce cost and morbidity of NAC. Alternatively, selecting patients most likely to respond to NAC will enrich the population of patients receiving and benefiting from NAC. Several possible biomarkers have been described including mutations in DNA repair genes *ATM*, *RBI*, and *FANCC*,(5) mutations in excision repair cross-complementation group 2 (*ERCC2*) gene,(6, 7) protein biomarkers,(8) and RNA subtyping of bladder cancer.(9, 10) Although difficulties exist in assessing the potential risks and benefits of incorporating molecular markers into decision-making regarding use of NAC, decision analysis modeling can improve our understanding of the efficacy and cost implications of using biomarkers to guide treatment. Furthermore, this model could serve as basis for rationale incorporation of emerging biomarkers into clinical decision making for complex oncology. In this study, we evaluated the cost-effectiveness (CE) of potential biomarkers to guide the use of NAC in patients with MIBC.

MATERIALS AND METHODS

A decision analysis model was developed using TreeAge Pro 2016 to evaluate the CE of different management approaches in locally-advanced, MIBC (T2-T4aN0M0). All patients were assumed eligible for cisplatin-based NAC. There are 3 treatment arms in the model (Figure 1): 1) patients who undergo RC alone, 2) patients who undergo unselected NAC followed by RC, and 3) patients who undergo biomarker-directed NAC followed by RC. The primary endpoint was the CE of different approaches for use of NAC based on 5-year OS. Baseline assumptions in the model were varied by $\pm 10\%$ to generate confidence intervals. One-way and two-way sensitivity analyses were used to evaluate the impact of different assumptions on outcomes of the model.

Defining the Patient Population

The National Cancer Database (NCDB) was used to estimate proportion of clinical T2 (78.9%), T3 (13.7%), and T4 (7.7%).(4) Survival data depends primarily on pathologic stage and there is considerable discrepancy between clinical and pathologic staging at the time of RC.(11) A multicenter study of 788 patients undergoing RC found pathologic upstaging and downstaging occurred in 42% and 22%, respectively.(11) The stage distribution of patients undergoing RC for non-metastatic, MIBC was corrected for pathologic staging (Table 1).

Estimating Patient Survival

The 5-year OS of patients undergoing RC alone was obtained from several sources. The SWOG 8710 study found a 5-year OS for pT0 patients of 85%⁽¹⁾ and a cohort of >1,000 patients who underwent RC at the University of Southern California (USC) found 85% 5-year OS for node-negative patients with pT0,pTa,pTis.⁽¹²⁾ In the same USC cohort, the 5-year OS for patients with pT1N0 was 76%, yielding an average 5-year OS of 81% for <pT2N0.⁽¹²⁾ The 5-year OS for stages pT2-T4 and pTanyN1-2 were obtained from a multicenter study of >2,700 RC cases.⁽¹³⁾

In order to determine the 5-year OS for each clinical stage, we used the expected distribution of pathologic stages for each clinical stage and multiplied by the expected 5-year OS for each pathologic stage (Table 1). Using this weighted-average approach, the 5-year OS for the entire cohort (cT2-T4) was 54.2%.

The survival benefit of NAC was estimated by a meta-analysis of 15 randomized clinical trials which indicated a decreased risk of all-cause mortality associated with cisplatin-based NAC (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.79-0.96).⁽³⁾ This translates into 13% fewer deaths with a 5-year OS for NAC of 60.2% (if 100% of eligible patients receive NAC).

Treatment Assumptions

In the unselected NAC arm, the model was tested assuming all or just a portion of patients accept NAC. An NCDB analysis of MIBC patients who underwent RC found that 20.9% received NAC in 2010.⁽⁴⁾ In some centers, NAC is only given in high-risk patients and the observed patterns of NAC utilization likely reflects this risk-adopted approach.⁽¹⁴⁾ We modeled a scenario of 20% of eligible patients receiving NAC. In the biomarker-directed NAC arm, all patients underwent biomarker testing. Those with a positive marker receive NAC and those with a negative marker receive RC alone. Since current markers are not perfect in their prediction of response, not every patient with marker alterations (positive marker) benefits from chemotherapy. The percent of responders based on prior clinical studies was incorporated into the model.

Biomarker Assumptions

For demonstrative purposes, we examined 3 potential biomarkers including genomic alterations in the DNA repair genes *ATM*, *RBI*, and *FANCC*,⁽⁵⁾ missense mutations in *ERCC2*,⁽⁶⁾ and RNA subtypes of bladder cancer.⁽⁹⁾

In the study by Plimack et al., 22 of 58 patients (38%) had an alteration in *ATM*, *RBI* or *FANCC* (biomarker-positive).⁽⁵⁾ The rate of these mutations in The Cancer Genome Atlas (TCGA) was identical at 38.1% (*ATM* 15.4%, *RBI* 21.1% and *FANCC* 1.6%).^(15–17) Of the 22 patients, 20 patients (91%) were pT1N0 at time of RC.

Data on performance of *ERCC2* was derived from a validation study by Liu et al. which revealed an *ERCC2* mutation in 10 of 48 patients (21%).⁽⁶⁾ The rate in the TCGA for *ERCC2* mutations was lower at 10.5% in a larger cohort so this rate was used in the model. ^(15–17) Of the biomarker-positive patients, 80% were pT1N0 at time of RC.

The impact of RNA subtyping on outcomes was based on an analysis by Choi et al. Basal, luminal, and p53-like subtypes constituted 32%, 33%, and 35% of the cohort and had a response to NAC (defined as pT1N0) of 47%, 62%, and 6%, respectively.(9) In the model we assumed that patients with basal and luminal subtypes would receive NAC for an average response of 55.6% and those with p53-like tumors would proceed to RC alone. Based on a recent analysis suggesting limited benefit of NAC for luminal subtypes, we also performed a separate model wherein only patients with basal subtype tumors undergo NAC.(10)

A recent study found that patients who underwent NAC and were found to still have residual disease at RC had significantly worse 5-yr recurrence-free survival (50% vs 63%; $p=0.01$), cancer specific survival (40% vs 59%; $p=0.003$), and OS (33% vs 48%; $p=0.02$) than pathologic stage-matched controls who underwent RC alone.(18) In the model, we similarly lowered OS in non-responders to biomarker-directed NAC by 31.25%.

Cost Assumptions

All patients were assumed to undergo RC. The average cost for cystectomy and complications within 90 days was obtained from >7,000 cystectomies using Surveillance, Epidemiology, and End Results Program (SEER)-Medicare linked data and estimated at \$33,000, including all Medicare and co-insurance reimbursement and patient-liability costs. (19)

The costs for NAC and adjuvant chemotherapy were estimated at \$10,500 for cisplatin-based regimens (gemcitabine/cisplatin or dose-dense methotrexate, vincristine, Adriamycin, cisplatin).(20) The cost of salvage therapy was complicated due to the recent approval of immune checkpoint inhibitors, for which there is insufficient cost data. A cost of \$77,000 was estimated based on other biologic regimens.(21) Patients receiving NAC and those with pT2N0 were assumed to not receive adjuvant chemotherapy, whereas 30% of those with chemo-naïve, non-organ confined disease were assumed to accept adjuvant chemotherapy. Similarly, 30% of those with non-organ confined disease were assumed to receive salvage chemotherapy. While a recent report found that use of adjuvant chemotherapy was around 20%, we used a higher rate as our model limited the use of adjuvant chemotherapy to patients with non-organ confined disease.(22) These assumptions were subsequently tested in the model to determine the impact of varying the rate of acceptance of adjuvant and salvage therapies.

Post-RC surveillance was modeled according to guidelines on imaging, lab, and urine studies from the National Comprehensive Cancer Network.(23) Cost of imaging studies was based on Medicare national average allowable fees.(24–26) Cost for laboratory tests were based on the Centers for Medicare & Medicaid Services Clinical Laboratory Fee Schedule. (27) A level 3 established outpatient physician visit was assumed at surveillance time-points. Based on these calculations, the cost (minimum-maximum) of surveillance was \$1,746.92 (\$1,164.64-\$2,329.28) for year 1, \$1,652.06 (\$1,114.92-\$2,189.20) for year 2, and \$543.08 per year for years 3-5.

Estimated costs of dying from bladder cancer were abstracted from an analysis of SEER-Medicare linkage data(28) which included all inpatient and outpatient claims among

beneficiaries dying of bladder cancer made in the last-year of life.(29) Adjusted for inflation, the cost of dying from bladder cancer was estimated at \$93,775.51 in 2017 dollars.

The cost of the marker was estimated at \$2,000. While the exact cost of sequencing varies between genetic tests, this was approximated between costs of commercially-available tests and the current cost of whole exome sequencing at our sequencing Core. This was modeled at varying costs and this cost will likely decrease over time.

RESULTS

The results of the model are shown in Table 2. The least effective strategy is RC alone with an average 5-year OS of 54.2% and mean survival of 2.71 years. For strategies of NAC prior to cystectomy without a biomarker, 5-year OS is 60.2% if all get NAC and 55.4% if only 20% accept NAC. In the biomarker-based approaches, the 5-year OS was 56%, 59% and 62.8% for arms using *ERCC2*, RNA subtyping, and mutations in the DNA repair genes *ATM*, *RBI*, and *FANCC*, respectively.

The overall cost of care was higher in arms that received NAC in large part based on the proportion of patients who received NAC. The most expensive strategy was based on subtyping since all had the cost of the marker and 65% had the added cost of chemotherapy. The most cost-effective strategy was based on DNA repair genes (\$31,482/life year). The least cost-effective strategy was based on RNA subtyping (\$35,794/life year). If NAC is only used in patients with basal subtype tumors then the overall cost is \$102,205 with an expected mean OS of 2.77 years and CE of \$36,897/life year.

A tornado diagram was created to evaluate the impact of different factors on the cost of bladder cancer care (Figure 2). The cost of dying has the highest impact on the model due to the high cost of the last year of life and the significant mortality rate. Unsurprisingly, the cost of RC had a high impact. Finally, the probability of receiving and cost of salvage treatment were next most influential on overall cost since salvage therapy (\$77,000) is much more expensive than adjuvant chemotherapy (\$10,500). Since there is insufficient data on the likelihood of receiving salvage treatments such as immune checkpoint blockade, we modeled the impact of 10%, 30%, 50% and 70% of patients receiving such therapies (Table 3). The cost can vary by as much as \$29,437 per patient. This has a greater impact on patients who do not receive NAC as they are more likely to have non-organ confined disease and require salvage therapy.

A two-way sensitivity analysis was conducted over a wide range of biomarker-positivity rates and ability of the biomarker to predict response to chemotherapy (Table 4). If no patients have an abnormal marker (0%) then no NAC is given and outcomes are similar to RC alone. However, costs are \$2,000 higher due to the cost of the marker. If 60% of patients have a positive marker and 60% of these patients have a response to NAC, the mean survival would be 2.99 years and the cost per patient would be \$104,307. On the other hand, a marker that is positive in 20% of patients and predicts a response rate of 80% would have a mean survival of 2.89 years and cost of \$98,793.

DISCUSSION

Despite level 1 evidence of a survival benefit of NAC in patients with MIBC, (1) multiple studies have demonstrated low utilization rates. There are concerns among physicians and patients about toxicity of therapy and possible delay in cystectomy. Recent studies have identified potential biomarkers such as DNA repair genes and RNA subtyping as predictive of response to NAC.(5, 6, 9) Utilizing biomarkers to enrich the response of patients undergoing NAC has the potential to increase the utilization of NAC in those patients most likely to respond and spare those unlikely to respond from potential toxicities associated with treatment.

In this study, a decision analysis model was utilized to compare the cost-effectiveness of strategies using a biomarker to determine which patients should undergo NAC versus unselected use of NAC or cystectomy alone. The most cost-effective strategy involved using DNA-repair genes which provided NAC to 38% of patients with 91% response rate. While we recognize that further studies are necessary to define the optimal marker for selecting patients for NAC, there are many efforts underway such as the SWOG 1314 trial. Our model is limited by the fact that the current literature still consists of small patient cohorts, however the 2-way sensitivity analysis we designed can predict the cost-effectiveness of any marker based on its performance (Table 4). One should also note that there are no direct comparisons of markers in the literature so the best marker combination cannot be extrapolated from current literature and will likely evolve over time. More recent studies suggest that the basal subtype benefits more from NAC than the luminal subtype with a suggestion that patients with luminal subtype tumors should undergo cystectomy without NAC.(10) Further data is necessary to adequately model this type of information since it is possible that NAC in some patients leads to worse outcomes due to a minimal benefit and delay in cystectomy. Refinement in clinical staging may better define the optimal patient to treat with NAC since it is known that patients with more advanced stage are more likely to benefit from NAC.(10) It is also possible that biomarkers will be beneficial in improving staging but this was beyond the scope of this model.(30)

The major cost that impacted the model was cost of dying which represents a significant proportion of total healthcare costs in the US.(31) Strategies that improve OS benefit significantly by reducing the cost of dying and avoiding salvage therapies, which more than compensate for the upfront cost of NAC. Furthermore, this study preceded the introduction of expensive treatments like immune checkpoint inhibitors that will likely raise costs. The proportion of patients who required salvage therapies significantly impacted the cost of care with as much as a \$29,437 difference in scenarios where 10% vs. 70% of the patients with non-organ confined disease received salvage treatments.

The implications of this study are significant. The use of NAC was found to be cost-superior to RC alone and strategies to enrich a population for responders is cost-effective. While the best biomarker for response to NAC is not established, this type of modeling demonstrates that even an imperfect biomarker can significantly improve cost-effectiveness over unselected use of NAC. Furthermore, it is known that many eligible patients are not

receiving NAC and that a biomarker for response may improve utilization by selecting patients most likely to respond.

The model created is based on assumptions which are limited by the strength of evidence. Some evidence is strong, including the benefits of NAC and outcomes of patients with bladder cancer, which are rooted in large population data or randomized trials. Other assumptions like the proportion of patients who will undergo adjuvant or salvage therapies are not as well established. Furthermore, it is difficult to model the potential benefits on survival of salvage therapies but these benefits would be similar between different arms of the study and are unlikely to impact results significantly. Finally, cost data is based on best available literature but can vary geographically and based on type of insurance. For the most part Medicare-based reimbursement was used since it is the most widely used cost metric nationally even though some patients will be younger than 65 years and will have private insurance. Despite these limitations, we feel that the proposed model should be considered an example of how to estimate the value of novel biomarkers in oncologic care.

CONCLUSIONS

A biomarker-based strategy using DNA repair genes (*ATM*, *RBI*, *FANCC*) to identify which patients with MIBC should undergo NAC was more cost-effective than unselected use of NAC or cystectomy alone.

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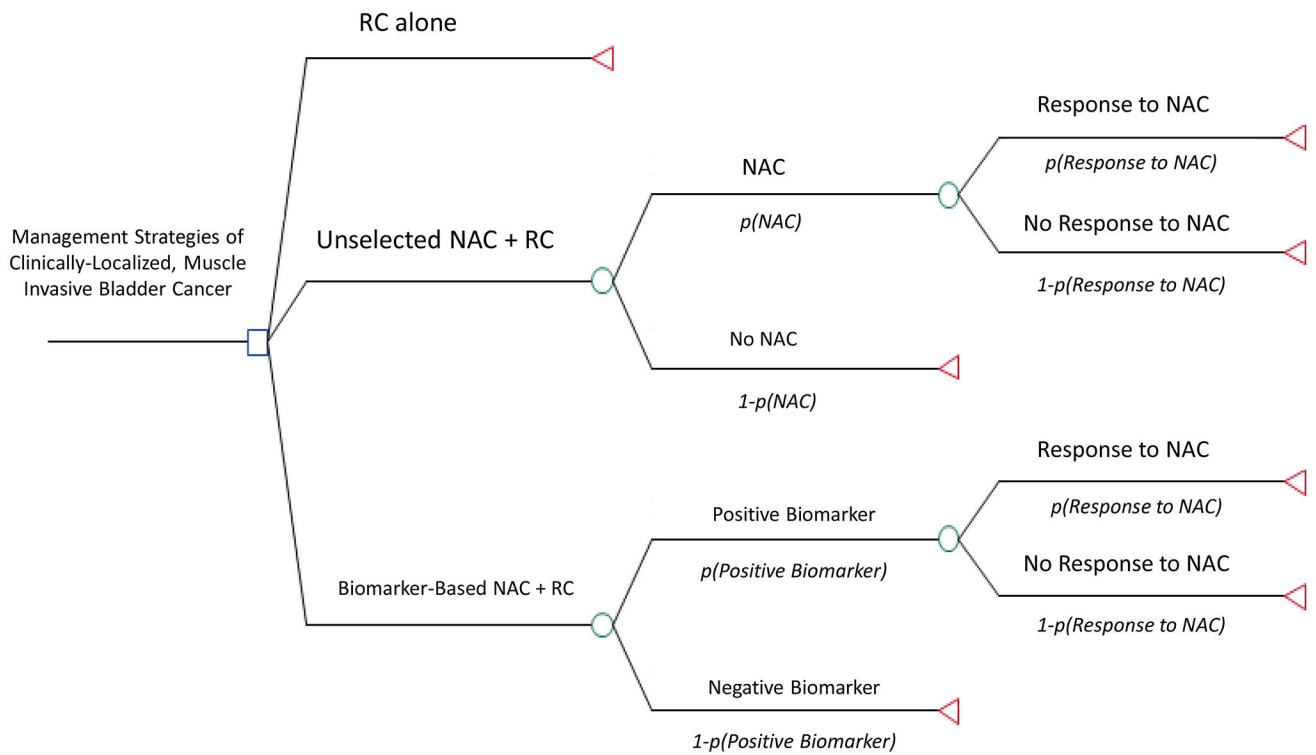


Figure 1.
 Decision Analysis Model.
 Abbreviation Key: RC = radical cystectomy; NAC = neoadjuvant chemotherapy; lower case p = probability.

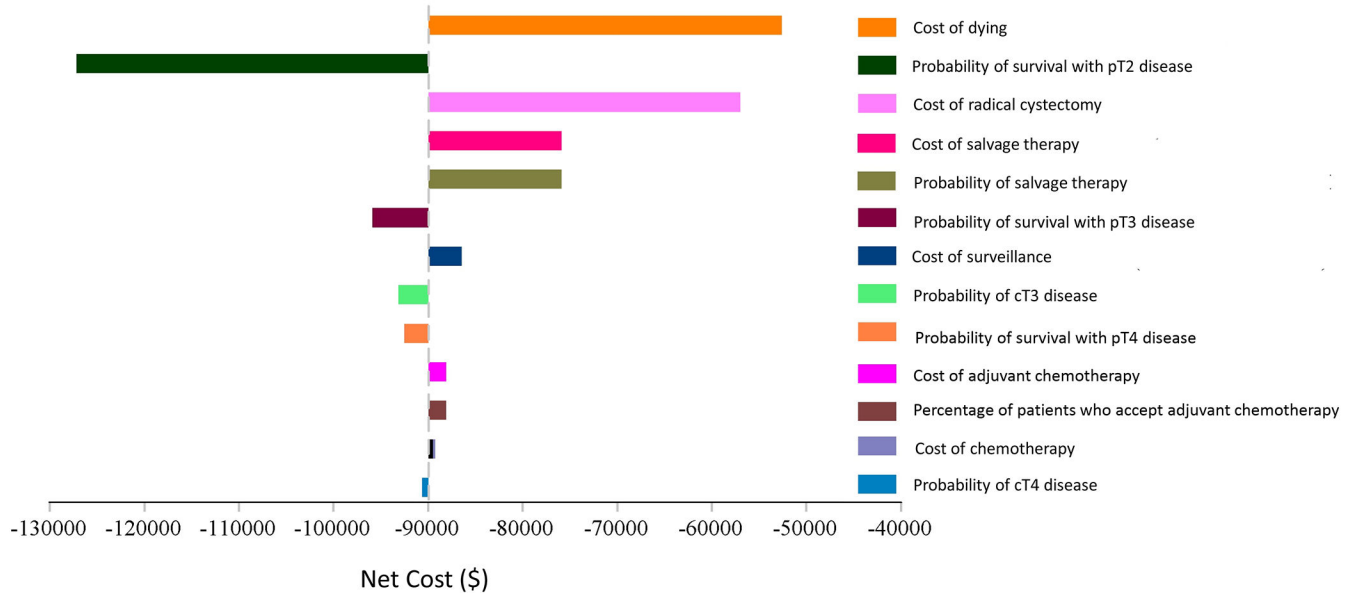


Figure 2.
Tornado Analysis of Variables Affecting Cost in the Model
Abbreviation Key: NAC = neoadjuvant chemotherapy
Interpretation of the tornado diagram

1. Variables with a wide bar indicate *value sensitive* variables, suggesting they have a higher impact on cost in the model. For example, the cost of dying has the highest impact on the model. This is also why survival for pT2 has such a large impact since higher mortality rates result in more cost.
2. The cost of radical cystectomy had a high impact since it impacts all patients.
3. The probability of getting and cost of salvage were next most influential on overall cost since salvage therapy at (\$77,000) is much more expensive than adjuvant chemotherapy (\$10,500).
4. Variables that did not have a significant impact on cost in the model (not shown) included the probability of receipt of NAC (in the unselected NAC arm), probability of response to NAC, probability of biomarker positivity, accuracy of the biomarker, cost of the biomarker, probability of survival in patients who respond to NAC, and cost of surveillance following radical cystectomy.

Table 1.

Calculation of Pathologic Stage and 5-Year Overall Survival Outcomes Based on Established Clinical Stage Distribution in Muscle-Invasive Bladder Cancer

Clinical Stage (%)	Pathological Stage Correction (%)					5-year OS (%)
	<T2N0	T2N0	T3N0	T4N0	TanyN+	
cT2 (78.9)	22.7	22.2	29.5	3.5	22.1	56.1
cT3 (13.7)	16.3	6.3	50.1	3.3	24	51.3
cT4 (7.7)	0	4.1	10.1	32.8	53	39.6
5-year OS (%)	81	65	50	47	31	

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Table 2.

Cost-Effectiveness According to Treatment Strategy

	5-year OS (%)	Mean OS (Years)	% Patients Undergoing NAC	Cost (\$) (Range [*])	Cost-Effectiveness (cost [\$] per life year) (Range [*])
Traditional Approaches					
Cystectomy Alone	54.2	2.71	0	95,552 (84,727-106,659)	35,259 (31,265-39,358)
Cystectomy + NAC [^]	60.2	3.01	100	96,708 (85,933-107,729)	32,129 (28,549-35,790)
Cystectomy + NAC ^{**}	55.4	2.77	20	95,783 (84,968-106,873)	34,579 (30,674-38,582)
Biomarker-Based Approaches					
DNA Repair Genes (<i>ATM, RBI, FANCC</i>)	62.8	3.14	38	98,855 (87,720-110,216)	31,482 (27,936-35,101)
<i>ERCC2</i>	56	2.80	10.5	98,204 (86,964-109,380)	35,072 (31,059-39,064)
RNA Subtyping (basal and luminal get NAC)	59	2.95	65	105,592 (93,648-117,696)	35,794 (31,745-39,897)

* Model was analyzed with all costs and probabilities of adjuvant and salvage +/- 10%

[^] Assuming 100% of eligible patients receive NAC

^{**} Only 20% of eligible patients actually receive neoadjuvant chemotherapy

Abbreviation Key: OS = overall survival; NAC = neoadjuvant chemotherapy

Table 3.

Modeling the Impact of Different Rates of Salvage Therapy on 5-Year Costs of Muscle-Invasive Bladder Cancer Management

	% Patients Undergoing Salvage Therapy for Non-Organ Confined Disease			
	10% salvage	30% salvage	50% salvage	70% salvage
Traditional Approaches				
Cystectomy Alone	\$86,146	\$95,552	\$104,958	\$114,364
Cystectomy + NAC [^]	\$88,526	\$96,708	\$104,892	\$113,075
Cystectomy + NAC [*]	\$86,622	\$95,783	\$104,945	\$114,106
Biomarker-Based Approaches				
DNA Repair Genes (<i>ATM, RBL, FANCC</i>)	\$89,772	\$98,855	\$107,939	\$117,022
<i>ERCC2</i>	\$88,839	\$98,204	\$107,569	\$116,934
RNA Subtyping	\$95,780	\$105,592	\$115,405	\$125,217

[^] Assuming 100% of eligible patients receive NAC

^{*} Only 20% of eligible patients actually receive neoadjuvant chemotherapy

Abbreviation Key: NAC = neoadjuvant chemotherapy

Table 4.

Two-Way Sensitivity Analysis of Cost and Median Overall Survival Based on Different Probability of Biomarker Positivity and Predictive Ability

Probability of Response to Chemotherapy if Biomarker is Positive	Probability of Biomarker Positivity				
	0%	20%	40%	60%	80%
40%	\$97,552	\$100,814	\$104,075	\$107,338	\$110,599
	2.71 years	2.71 years	2.72 years	2.73 years	2.73 years
60%	\$97,552	\$99,803	\$102,055	\$104,307	\$106,559
	2.71 years	2.80 years	2.90 years	2.99 years	3.08 years
80%	\$97,552	\$98,793	\$100,035	\$101,277	\$102,518
	2.71 years	2.89 years	3.07 years	3.25 years	3.43 years
100%	\$97,552	\$97,783	\$98,015	\$98,246	\$98,478
	2.71 years	2.98 years	3.25 years	3.51 years	3.78 years

Top row in each cell represents estimated costs at 5-years, bottom row of each cell represents median overall survival.

Assumes marker cost of \$2000 for all patients

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