12-1-2022

Risk-Based Assessment Of the Impact Of Intravesical Therapy on Recurrence-Free Survival Rate Following Resection of Suspected Low-grade, Non-muscle-invasive Bladder Cancer (NMIBC): A Southwest Oncology Groups (SWOG) S0337 Posthoc Analysis

Nicholas J. Corsi
Henry Ford Health, ncorsi1@hfhs.org

Edward M. Messing

Akshay Sood
Henry Ford Health, ASOOD1@hfhs.org

Jacob Keeley
Henry Ford Health, JKeeley2@hfhs.org

Chandler Bronkema
Henry Ford Health, cbronke1@hfhs.org

See next page for additional authors

Recommended Citation
Corsi NJ, Messing EM, Sood A, Keeley J, Bronkema C, Rakic N, Jamil M, Dalela D, Arora S, Piontkowski AJ, Majdalany SE, Butaney M, Rakic I, Li P, Menon M, Rogers CG, and Abdollah F. Risk-Based Assessment Of the Impact Of Intravesical Therapy on Recurrence-Free Survival Rate Following Resection of Suspected Low-grade, Non-muscle-invasive Bladder Cancer (NMIBC): A Southwest Oncology Groups (SWOG) S0337 Posthoc Analysis. Clin Genitourin Cancer 2022; 20(6):e498-e505.

Authors

Nicholas J. Corsi, Edward M. Messing, Akshay Sood, Jacob Keeley, Chandler Bronkema, Nikola Rakic, Marcus Jamil, Deepansh Dalela, Sohrab Arora, Austin J. Piontkowski, Sami E. Majdalani, Mohit Butaney, Ivan Rakic, Pin Li, Mani Menon, Craig G. Rogers, and Firas Abdollah

Original Study

Risk-Based Assessment Of the Impact Of Intravesical Therapy on Recurrence-Free Survival Rate Following Resection of Suspected Low-grade, Non-muscle-invasive Bladder Cancer (NMIBC): A Southwest Oncology Groups (SWOG) S0337 Posthoc Analysis

Nicholas J. Corsi,[1,2] Edward M. Messing,[3] Akshay Sood,[1,4] Jacob Keeley,[1] Chandler Bronkema,[1,5] Nikola Rakic,[1,6] Marcus Jamil,[1,7] Deepansh Dalela,[1,7] Sohrab Arora,[1,7] Austin J. Piontkowski,[1,2] Sami E. Majdalany,[1] Mohit Butaney,[1] Ivan Rakic,[1,2] Pin Li,[1,7] Mani Menon,[1,8] Craig G. Rogers,[1,7] Firas Abdollah[1,7]

Abstract

We identify novel risk groups of patients with suspected low-grade nonmuscle invasive bladder cancer (NMIBC). We utilize regression-tree analysis to characterize those who maximally benefit from intravesical chemotherapy following transurethral resection of bladder tumor (through recurrence-free survival). Cancer control outcomes vary between these risk groups, and the maximum benefit is observed in older patients with a single tumor.

Background: Nonmuscle invasive bladder cancer (NMIBC) has an elevated risk of recurrence, and immediate postresection intravesical instillation of chemotherapy (IVC) significantly reduces the risk of recurrence. Questions remain about which subpopulation may maximally benefit from IVC. Our aim was to develop risk groups based on recurrence risk in NMIBC, and then evaluate the impact of a single, postoperative instillation of IVC on the subsequent risk of recurrence for each risk group. **Material and Methods:** Using the SWOG S0337 trial cohort, we performed a posthoc analysis of 345 patients who were diagnosed with suspected low-grade NMIBC, underwent transurethral resection of the bladder tumor (TURBT), and received post-operative IVC (gemcitabine vs. saline). Using regression tree analysis, the regression tree stratified patients based on their risk of recurrence into low-risk – single tumor and aged < 57 years, intermediate-risk – single tumor and aged ≥ 57 years, and high-risk – multiple tumors. We used Cox proportional hazard models to test the impact of recurrence-free rate, and after adjustment to available covariates. **Results:** Median age of the cohort was 66.5 (IQR: 59.7-75.8 years) with 85% of patients being males. Median overall follow-up time was 3.07 years (IQR: 0.75-4.01 years). When testing the impact of treatment in each risk group separately, we found that patients in the intermediate-risk treated with gemcitabine had a 24-month recurrence free rate of 77% (95% CI: 68%-86%) vs. 59% (95% CI: 49%-70%) in the saline group. This survival difference was confirmed on multivariable analysis (hazard ratio: 0.39, 95% CI: 23%-66%, $P < 0.001$). This group represented 53% of our cohort. Conversely, we did not observe a significant difference in recurrence-free survival among patients in the low- ($P = 0.7$) and high-risk ($P = 0.4$) groups.

[1]Vattikuti Urology Institute Center for Outcomes Research, Analytics and Evaluation (VCORE), Henry Ford Hospital, Detroit, MI
[2]Wayne State University School of Medicine, Detroit, MI
[3]Department of Urology, University of Rochester, Rochester, NY
[4]Department of Urology, University of Texas MD Anderson Cancer Center, Houston, TX
[5]Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA
[6]Department of Urology, Baylor College of Medicine, Houston, TX
[7]Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI
[8]Department of Urology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY

Submitted: Apr 25, 2022; Revised: Jun 3, 2022; Accepted: Jun 20, 2022; Epub: 25 June 2022

Address for correspondence: Firas Abdollah, MD, Vattikuti Urology Institute, Henry Ford Hospital, 2799 W. Grand Boulevard, Detroit, Michigan, USA 48202.
E-mail contact: fabdoll1@hfhs.org, firas.abdollah@gmail.com

1558-7673/$ - see front matter
https://doi.org/10.1016/j.clgc.2022.06.015

Conclusion: Our findings indicate that older patients with a single tumor of suspected low-grade NMIBC at TURBT maximally benefit from immediate postresection IVC (gemcitabine).

Clinical Genitourinary Cancer, Vol. 20, No. 6, e498–e505 © 2022 Elsevier Inc. All rights reserved.
Key Words: Risk groups, Chemotherapy, Gemcitabine, TURBT

Introduction

Globally, there are approximately 390,000 new diagnoses of bladder cancer a year[1], and approximately 70% of new bladder cancer cases are classified as non-muscle-invasive bladder cancer (NMIBC) at diagnosis.[2] In these individuals, tumor recurrences are frequent after initial resection, which necessitates repeat treatment.[3] Previous studies observed that many of these patients experience significant discomfort, worry, and anxiety related to their disease progression.[4] Moreover, urothelial cancer is one of the most costly tumors to treat over a patient's lifetime.[5] In the United States, estimates show that the cost of diagnosis and follow-up of individuals diagnosed with superficial bladder cancer, even after excluding the treatment and costs associated with progressive disease, accrue to over $157.5 million over 5 years.[5]

Given the aforementioned issues, and in efforts to decrease the recurrence risk, the 2020 American Urological Association (AUA)/Society of Urologic Oncology (SUO) Joint Guidelines on the Diagnosis and Treatment of Non-Muscle Invasive Cancer now recommends a single postoperative instillation of intravesicular chemotherapy (eg, gemcitabine, mitomycin C) within 24 hours of resection of bladder tumor (TURBT) in patients with suspected or known low- or intermediate-risk bladder cancer.[6] Even with these recommendations, however, nationwide cross-sectional sampling demonstrates wide variation in the use of intravesical chemotherapy and the use of this treatment modality in NMIBC remains relatively low.[7] This might be due to several factors including the lack of a standardized risk-stratification that correlates well with the risk of recurrence,[8] limited resources, as well as the potential of over-treatment, and causing unnecessary side effects. Unfortunately, in the current clinical setting, the vast majority of decisions for NMIBC and bladder cancer, in general, are made without consultation of a predictive tool or decision aid.[9]

To address this void, and in an effort to improve chemotherapeutic agent use, and deliver individualized care, we sought to identify which patients will benefit the most from postoperative intravesical chemotherapy among those with suspected low-grade NMIBC. In this study, we use a decision-tree learning method to develop risk groups based on the risk of recurrence. Thereafter, we evaluate the impact of a single, postoperative instillation of intravesical chemotherapy (IVC) on the risk of subsequent recurrence in each of the risk groups.

Methods

Data Source, Study Population, and Study Period

This posthoc analysis utilizes the data of the Southwest Oncology Group's (SWOG) trial S0337 (National Clinical Trial Number 00445601). This study was deemed exempt from review by the Henry Ford Institutional Review Board (IRB). This randomized controlled trial was performed across 23 sites over a duration of 10 years and followed patients for a median of 4 years. The primary objective was to determine if a single, immediate post-TURBT instillation of gemcitabine reduces bladder cancer recurrence, compared with saline, for newly diagnosed bladder cancer (criteria was <2 prior low-grade non-muscle invading urothelial carcinomas and no prior nonurothelial carcinomas for 18 months before index TURBT).[10] Exclusion criteria from the dataset include patients with prior nonurothelial and/or, muscle-invasive bladder cancer, or those who received intravesical therapy within 6 months. Our study did not exclude patients who were eventually determined to have high-grade disease on histology, as the original trial was created to replicate the standard of care in the US, in order to maximize the study's relevance). Therefore, in-office biopsy before TURBT was not permitted. Our study considered all enrolled patients, even those who would not go on to have the expected histology (low-grade stage Ta or T1 urothelial cancer) because eligibility was based on cystoscopic appearance, not confirmatory histology. Specifically, 406 patients were enrolled and randomized in the study. Three hundred and eighty-three received TURBT, and these were included in our regression tree analysis. Of those patients, 345 went on to receive either gemcitabine or saline. Thirty-eight patients did not receive the study drug instillation, either due to depth of TURBT, resection extent, and/or other logistical reasons, which is a proportion similar to previous reports.[10] The 345 patients who ultimately received gemcitabine or saline (as randomized) were included in our posthoc treatment analysis.

Variable Definitions and Patient Assessment

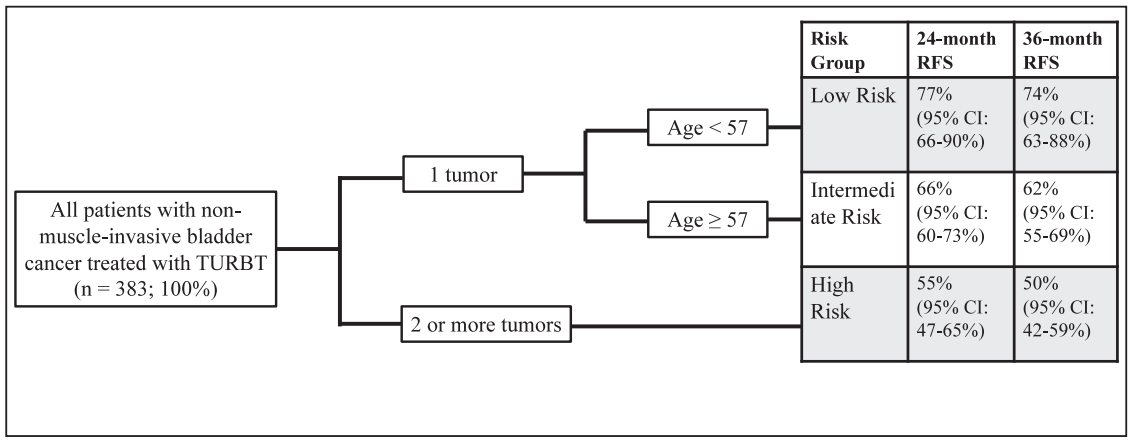
For all patients, the following variables were extracted: age, sex, race, first occurrence vs. recurrent disease, one vs. >1 tumor, Zubrod performance status, smoking history, and history of prior intravesical therapy for bladder cancer (Adriamycin, BCG, or mitomycin). Finally, the randomization variable, 1 dose of gemcitabine post-TURBT vs. saline, was also extracted.

Our endpoint consisted of bladder cancer recurrence, which was histologically confirmed as per the original SWOG S0337 protocol. Time to recurrence was measured from the date of registration to the date of the first observation of recurrent disease. With respect to time to recurrence, patients without recurrence were censored at the time of their last cystoscopy. Patients who died or had cystectomy without recurrence were censored for the purpose of our analysis.

Statistical Analysis

Descriptive statistics consisted of medians and interquartile ranges (IQRs) for continuous variables, while frequency and proportions were reported for categorical variables. The t test and χ^2 test were used to compare continuous, and categorical variables, respec-

Figure 1 A risk stratification tool based on regression tree analysis from 383 patients with nonmuscle-invasive bladder cancer treated with TUBRT. RFS = recurrence free survival



tively. Our statistical analysis consisted of several steps. First, we classified patients into risk groups based on their risk of recurrence using a regression tree analysis for censored data. This applies a standard and recursive algorithm to sequentially divide a cohort of patients into risk-based subgroups. In this process, separation between the sub-groups' class-specific survival curves is maximized.[11] The regression tree algorithm chooses the optimal sequence of classifications, as defined by a hierarchy of prognostic factors.[12] All available variables, except for the randomization variable (gemcitabine vs. saline) were tested in the tree analysis.

Second, we utilized Kaplan-Meier curves to depict NMIBC recurrence-free survival in each of the novel risk groups generated by the tree analysis. Then, in each risk group, we stratified patients based on the gemcitabine treatment status and depicted their survival. Log-rank test was used to verify statistical significance.

Third, Cox regression analysis evaluated the impact of gemcitabine treatment status on recurrence-free survival in each risk group after adjusting for available confounders. Finally, a sensitivity analysis was performed in patients with completed TURBT, who received randomized drug instillation, and had confirmed low-grade pathology on histology. Statistical analyses were performed using the R statistical package (v.4.0.3). All tests will be 2-sided, and a P value of < 0.05 will be considered significant.

Results

Descriptive Analysis

Descriptive statistics of patient characteristics are summarized in Table 1. The median age of the cohort was 66.5 (IQR: 59.7-75.8) with 85% of patients being males. Median follow-up for the entire cohort was 3.07 years (IQR: 0.75-4.01).

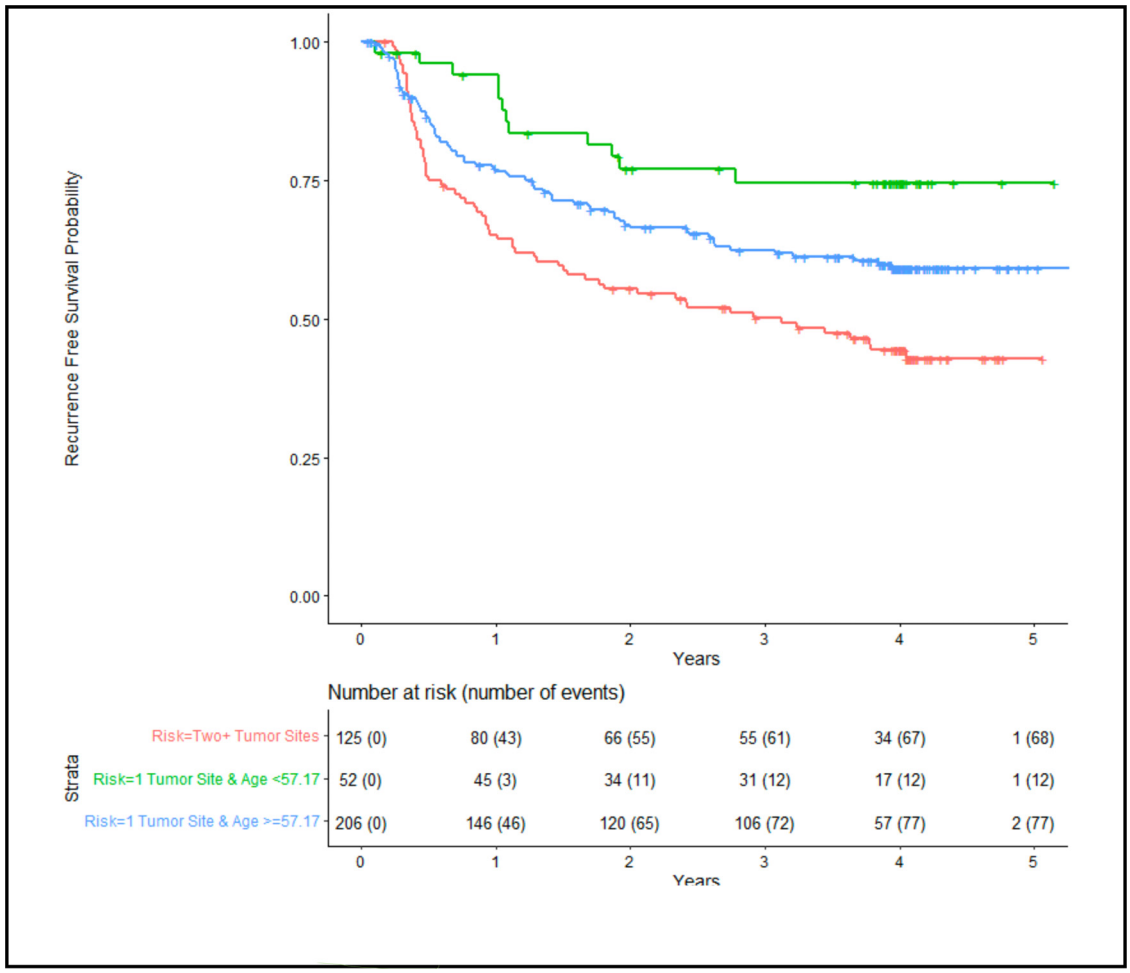
Regression Tree Analysis

Regression tree analysis found the number of tumors and age to be the 2 most important stratifying variables. Grade, as a variable, was not selected as a stratifying factor by the tree. The regression tree categorized patients into the following three risk groups based on their recurrence risk (Figure 1): low-risk – 1 tumor and age < 57, intermediate-risk – 1 tumor and aged ≥ 57 years, and high-risk – 2 or more tumors, regardless of age. The low-, intermediate-, and high-risk groups represented 14%, 53%, and 33% of the entire cohort, respectively. The 24-month recurrence-free survival rate was 64% (95% CI: 59%-69%) in the entire cohort, and it was 77%

Table 1 Patient Characteristics and Descriptive Statistics of the 345 Patients Who Received TURBT and Drug Instillation (Gemcitabine vs. Saline Only)

Variable		Overall
Age (mean, SD)		67.2 (11.1)
Race (%)	White	315 (91.3)
	Black	13 (3.8)
	Asian	8 (2.3)
	Native	2 (0.6)
	Unknown	7 (2.0)
Treatment Label (%)	Gemcitabine	168 (48.7)
	Saline only	177 (51.3)
Occurrence (%)	First occurrence	207 (60.0)
	Recurrent disease	138 (40.0)
Number of Tumors (%)	One tumor	230 (66.7)
	Two or more tumors	115 (33.3)
Zubrod Performance Status (%)	0	275 (79.7)
	1+	70 (20.3)
Smoking History (%)	Current	83 (24.1)
	Former	172 (49.9)
	Never	87 (25.2)
	N/A	3 (0.9)
Prior Intravesical Treatment History (%)	Yes	72 (20.9)
	No	273 (79.1)

Figure 2 Kaplan-Meier (KM) curve for recurrence-free survival probability after stratification into the three risk groups, according to the risk stratification tool



(95% CI: 66%-90%), 66% (95% CI: 60%-73%), and 55% (95% CI: 47%-65%) in the low-, intermediate-, and high-risk groups respectively (Figure 2).

Impact of Treatment

When evaluating the impact of treatment in each risk group separately, we found that in patients with intermediate-risk, the 24-month recurrence-free survival rate was 77% (95% CI: 68%-86%) in the gemcitabine group vs. 59% (95% CI: 49%-70%) in the saline group (log-rank $P = 0.002$, Figure 3). The beneficial impact on recurrence was confirmed on multivariable analysis in the intermediate-risk group, where patients who received gemcitabine had a more favorable recurrence risk than their saline counterparts (hazard ratio [HR]: 0.39, 95% CI: 0.23-0.66, $P < 0.001$) (Table 2). Conversely, we did not observe a significant difference in recurrence-free survival among patients in the low- (24-month recurrence-free survival rate: 82% vs. 71%, $P = 0.7$) and high-risk groups (24-month recurrence-free survival rate: 58% vs. 51%, $P = 0.4$), when treated with gemcitabine vs. saline. Similar results were observed in multivariable analysis (Table 2).

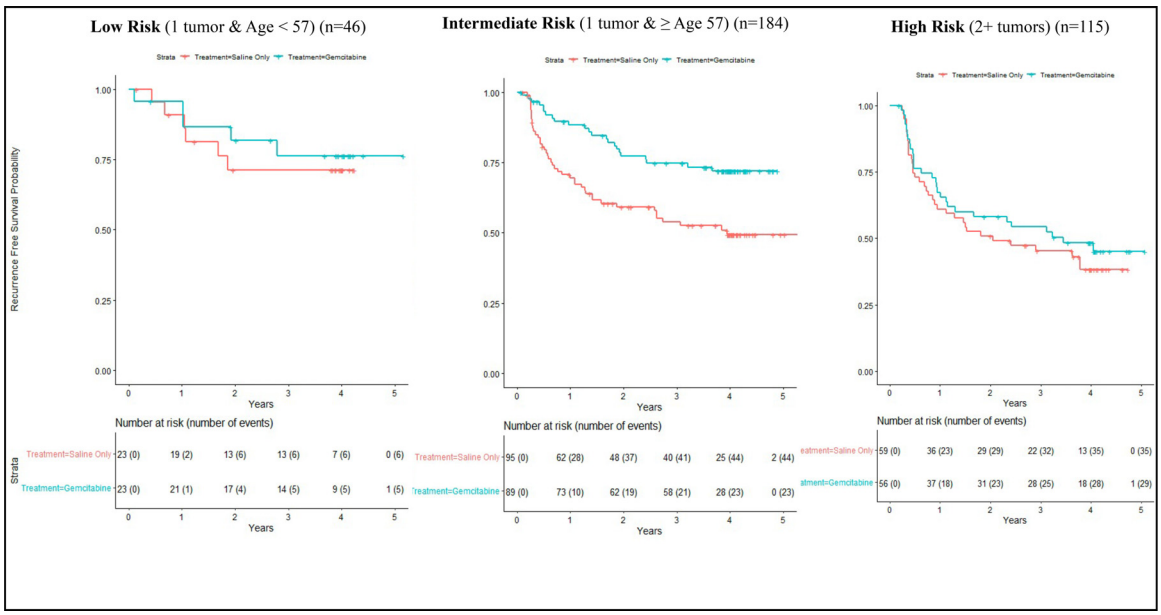
Sensitivity Analysis

We verified the validity of our results in the 215 patients who were found to have low-grade pathology on histology. Supplementary Tables 1 and 2 provide a detailed description of the risk group cohorts with confirmed low-grade tumors as well as sensitivity analysis outcomes. When assessing the impact of treatment, the recurrence free survival rate was again statistically significant only in the intermediate-risk group ($P = 0.03$, Supplementary Table 2). It is important to note, however, that while not statistically significant, the high-risk group very strongly approached a difference in the histologically confirmed low-grade population, at a P-value of 0.052 (Supplementary Table 2).

Discussion

Almost 60% of patients with NMIBC have recurrent cancer after TURBT,[13] which greatly influences surveillance schedules.[3] This

Figure 3 Kaplan-Meier (KM) curve for recurrence-free survival probability evaluating the impact of immediate postresection intravesical gemcitabine vs. saline, in the suspected low-grade cohort (n = 345) and histologically confirmed low-grade subgroup (sensitivity analysis, n = 215)



leads to a psychological and financial burden on patients, as there is an estimated cost of $96,000 to $187,000 per patient from diagnosis to death with NMIBC in the US.[5] Gemcitabine can reduce the risk of recurrence, but its utilization on a national level is limited at best.[14,15] In this study, we try to identify patients who would benefit the most from such treatment in an effort to optimize and individualize its utilization in the right patients, while avoiding unnecessary costs and potential side effects in those who are unlikely to benefit from it. However, with previous historically low rates of disease recurrence in low-grade papillary stage Ta NMIBC, clinicians must consider limiting the overuse of aggressive surveillance testing.[16] Currently, the European Organization for Research and Treatment of Cancer (EORTC) and Spanish Urological Club for Oncological Treatment (CUETO) risk tables are considered some of the most popular and established models to estimate recurrence in NMIBC,[17] but they have been reported to overestimate risk (poor stratification for recurrence),[18,19] underlining the need for improvements in predictive models.[20] To our knowledge, there is no multivariable, regression tree-derived, risk-stratification tool that estimates recurrence based on patient-specific clinical characteristics with NMIBC or estimates response to intravesical chemotherapy. In this study, we were able to identify risk groups with distinct oncological outcomes and differentiate responses to postoperative intravesical chemotherapy.

Our findings indicate that the main beneficial impact of immediate postresection instillation of intravesical gemcitabine is derived in patients who have a single tumor and age ≥ 57 years. Conversely, in patients with single tumors and age < 57, there was no significant benefit observed, potentially because these patients have a very favorable outcome regardless. Likewise, a nonbenefit of gemcitabine was observed in patients with 2 or more tumors. It is possible that the disease burden in these cases excludes the effectiveness of a single dose of gemcitabine.

Our findings may be applicable to many patients, as of all patients with newly diagnosed NMIBC, most (70%) present as stage Ta.[19] Our posthoc analysis of the SWOG S0337 study evaluated outcomes from all patients with suspected low-grade, stage Ta or T1 bladder cancer. The results of our sensitivity analysis demonstrate that our risk groups are arguably applicable to both low-grade, as well as high-grade NMIBC. This is because grade was not selected by regression tree analysis. The sensitivity analysis of patients with a confirmed low-grade disease on final histology, who received either gemcitabine or saline after TURBT, demonstrated the same group differences (Supplementary Table 2). While not statistically significant, however, the high-risk group very strongly approached a difference at $P = 0.052$. Our findings seem to corroborate previous reports in the literature. For example, a retrospective study determined that gemcitabine intravesical chemotherapy is an independent protective factor for recurrence, with a recurrence rate of 8.3% over a median follow-up of 34.8 months. The majority of the patients in this series were ≥ 65 with a single tumor.[21] This is similar to our intermediate-risk cohort. Likewise, in the original SWOG S0337 study, the authors found that immediate intravesical chemotherapy significantly reduced the risk of recurrence, with a 4-year recurrence rate of 35% in gemcitabine group vs. 47% in the saline group. Our analysis shows that most of the benefit is probably

Table 2 Univariable Cox Model Testing Treatment on Recurrence-Free Survival; Multivariable Cox Proportional Hazards Regression Analysis Testing Treatment on Recurrence Free Survival, in the Presence of Age, Race, Smoking History, Occurrence, and Prior Intravesical Treatment, Stratified by Risk Group

Variable		Univariable Analysis			Multivariable Analysis		
High Risk		**Hazards Ratio**	**95% CI**	***P* Value**	**Hazards Ratio**	**95% CI**	***P* Value**
Treatment	Gemcitabine	0.81	0.49 - 1.33	0.41	0.82	0.49 -1.35	0.44
	Saline	-	-	-	-	-	-
Age		1.00	0.98 - 1.02	0.75	1.00	0.98 - 1.03	0.46
Race	White	3.04	0.42 - 21.93	0.27	2.49	0.32 - 19.07	0.37
	Other	-	-	-	-	-	-
History of Smoking	Current	1.81	0.81 - 4.04	0.14	2.17	0.94 - 5.02	0.06
	Former	1.85	0.89 - 3.85	0.09	1.66	0.79 - 3.50	0.17
	Never	-	-	-	-	-	-
Occurrence	Recurrent disease	1.67	0.99 - 2.80	0.05	1.65	0.89 - 3.05	0.10
	No history	-	-	-	-	-	-
Prior intravesical therapy	Prior	1.30	0.77 - 2.19	0.32	0.91	0.48 - 1.71	0.77
	None	-	-	-	-	-	-
Intermediate Risk		*Hazards Ratio*	*95% CI*	*P Value*	*Hazards Ratio*	*95% CI*	*P Value*
Treatment	Gemcitabine	0.45	0.27 - 0.75	0.002	0.39	0.23 - 0.66	<0.001
	Saline	-	-	-	-	-	-
Age		0.98	0.95 - 1.01	0.20	0.96	0.93 - 1.00	0.07
Race	White	0.94	0.34 - 2.59	0.91	0.71	0.25 - 2.00	0.51
	Other	-	-	-	-	-	-
History of Smoking	Current	0.79	0.38 - 1.64	0.52	0.74	0.34 - 1.60	0.45
	Former	0.94	0.53 - 1.65	0.83	1.13	0.64 - 2.01	0.65
	Never	-	-	-	-	-	-
Occurrence	Recurrent disease	1.28	0.78 - 2.10	0.32	1.09	0.56 - 2.09	0.79
	No history	-	-	-	-	-	-
Prior intravesical therapy	Prior	1.91	1.10 - 3.31	0.02	2.04	1.01 - 4.12	0.04
	None	-	-	-	-	-	-
Low Risk		*Hazards Ratio*	*95% CI*	*P Value*	*Hazards Ratio*	*95% CI*	*P Value*
Treatment	Gemcitabine	0.76	0.23 - 2.50	0.65	1.16	0.23 - 5.91	0.85
	Saline	-	-	-	-	-	-
Age		1.15	0.96 - 1.37	0.11	1.16	0.94 - 1.44	0.15
Race	White	2.35	0.29 - 18.6	0.41	1.09	0.11 - 10.6	0.93
	Other	-	-	-	-	-	-
History of Smoking	Current	0.47	0.05 - 4.25	0.25	1.65	0.34 - 7.79	0.52
	Former	2.10	0.59 - 7.45	0.50	0.53	0.05 - 5.40	0.59
	Never	-	-	-	-	-	-
Occurrence	Recurrent disease	1.29	0.38 - 4.41	0.68	1.34	0.20 - 8.72	0.75
	No history	-	-	-	-	-	-
Prior intravesical therapy	Prior	1.09	0.23 - 5.05	0.91	0.74	0.07 – 7.48	0.80
	None	-	-	-	-	-	-

derived from an improvement in recurrence among patients with an intermediate risk, as demonstrated by our novel stratification tree. The variables that our regression tree has selected to stratify patients are in line with prior literature, as the amount of tumors has continuously been reported to be one of the most important prognostic factors for recurrence.[13,22] Additionally, in previous studies evaluating risk factors for recurrence, albeit, in a Chinese cohort, the number of lesions and tumor size were found to be significantly associated with short-term recurrence (<1 year from TURBT).[23] Unfortunately, the original trial did not capture and report tumor size for every patient. As a result, this prognostic variable was not considered in regression tree analysis and is a limitation. Interestingly, age was not significant on multivariable analysis for recurrence.

Taken together, our study can potentially help educate physicians and patients regarding the risk of recurrence in the heterogeneous spectrum of NMIBC. Regression trees have been utilized successfully in the setting of other genitourinary malignancies.[24] The benefits of regression tree analysis allowed us to explore the longitudinal, robust, phase III blinded SWOG S0337 data by identifying subgroups, and uncovering interactions or effect modifications among bladder cancer prognostic factors.[24] Regression analysis is not affected by outlying observations, and the results of the regression tree analysis are presented as a decision tree, which is far more intuitive and easier to interpret for patients, compared to predictive models.

Despite these strengths, our study is not without limitations. We recognize the inherent limitations of posthoc, observational analysis. As our study design is a retrospective analysis in nature, we cannot fully recommend treatment based on these new risk groups alone. To be clear, we are not suggesting only using IVC in intermediate risk patients and withholding it from high and low-risk patients. Our primary goal was to characterize those who benefit the greatest through RFS. The small sample size (as illustrated by the 31 patients in the low-risk subgroup on sensitivity analysis) is a significant limitation of the study design, and our results herein are rather hypothesis-generating. As such, the risk groups should be rigorously re-tested in larger samples and externally validated before consideration of application to practice. Additionally, patients who participated in the original SWOG S0337 trial should theoretically be a random sample from the population seen in clinical practice, and within the limitation of the selection criteria of the specific trial, should be representative of the real-world patients. However, to the best of our knowledge, no study has tested the external validity of the SWOG S0337 trial, and future efforts should focus on this. Additionally, there may be unobserved confounders within each of the groups, even though we adjusted our analyses for all available covariates.

Conclusion

Our findings indicate that patients with suspected low-grade NMIBC can have very different cancer control outcomes, based on their age and number of lesions. Our novel multivariable risk classification tool provides an accurate estimate of recurrence-free survival rates and can be used to improve patient counseling and build upon the growing evidence to guide intravesical chemotherapy and subsequent follow-up. Further external validation studies are needed to support the recommended risk stratification groups before treatment recommendations can be definitively made.

Clinical Practice Points

- What is Already Known About This Subject?
  Level-one evidence shows intravesical chemotherapy (Gemcitabine) increases recurrence-free survival in patients with suspected low grade nonmuscle invasive bladder cancer (NMIBC). However, even in the setting of national guideline recommendations, nationwide cross-sectional sampling demonstrates wide variation in the use of intravesical chemotherapy (IVC) and the use of treatment for NMIBC remains relatively low.
- What Are the New Findings?
  Therefore, this study proposes regression-tree analysis generated nonmuscle-invasive bladder cancer risk groups (low-, intermediate-, and high-risk) that may significantly benefit from intravesical chemotherapy following transurethral resection of bladder tumor. On posthoc analysis, the main beneficial impact of immediate postresection instillation of intravesical gemcitabine is those with a single tumor and older (aged $\geq$ 57 years).
- How Might It Impact on Clinical Practice in the Foreseeable Future?
  Following external validation, our novel multivariable risk classification tool provides an accurate estimation of recurrence-free survival rates and can be used to improve patient counseling and subsequent chemotherapy follow-up. Our results indicate which risk profile of patients may maximally benefit from intravesical chemotherapy, while avoiding the unnecessary side effects of those who would not likely benefit.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

None of the authors have any relevant disclosures, and none of the authors have any financial or nonfinancial interests that may be relevant to the submitted work.

Acknowledgments

This manuscript was prepared using data from Datasets from the NCTN Data Archive of the National Cancer Institute's (NCI's) National Clinical Trials Network (NCTN). Data were originally collected from clinical trial NCT number NCT00445601. All analyses and conclusions in this manuscript are the sole responsibility of the authors and do not necessarily reflect the opinions or views of the clinical trial investigators, the NCTN, or the NCI.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2022.06.015.

References

1. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder cancer incidence and mortality: a global overview and recent trends. *Eur Urol*. 2017;71(1):96–108.
2. Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. *Urology*. 2005;66(6 Suppl 1):4–34.
3. Donat SM. Evaluation and follow-up strategies for superficial bladder cancer. *Urol Clin North Am*. 2003;30(4):765–776.
4. Koo K, Zubkoff L, Sirovich BE, et al. The burden of cystoscopic bladder cancer surveillance: anxiety, discomfort, and patient preferences for decision making. *Urology*. 2017;108:122–128.
5. Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R. The health economics of bladder cancer: a comprehensive review of the published literature. *Pharmacoeconomics*. 2003;21(18):1315–1330.
6. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. *J Urol*. 2016;196(4):1021–1029.
7. Del Giudice F, van Uem S, Li S, et al. Contemporary trends of systemic neoadjuvant and adjuvant intravesical chemotherapy in patients with upper tract urothelial carcinomas undergoing minimally invasive or open radical nephroureterectomy: analysis of US claims on perioperative outcomes and health care costs. *Clin Genitourin Cancer*. 2022;20(2):198.e1–198.e9.
8. Downs TM, Weissert JA, Ravvaz K. Can we improve nonmuscle invasive bladder cancer guideline adherence with smarter risk stratification? *J Urol*. 2018;200(4):706–708.

9. Chamie K, Saigal CS, Lai J, et al. Compliance with guidelines for patients with bladder cancer: variation in the delivery of care. *Cancer*. 2011;117(23):5392–5401.
10. Messing EM, Tangen CM, Lerner SP, et al. Effect of Intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade non-muscle-invasive bladder cancer on tumor recurrence: SWOG S0337 randomized clinical trial. *JAMA*. 2018;319(18):1880–1888.
11. Segal MR. Regression trees for censored data. *Biometrics*. 1988;44(1):35.
12. Abdollah F, Sun M, Suardi N, et al. A novel tool to assess the risk of urinary incontinence after nerve-sparing radical prostatectomy. *BJU Int*. 2013;111(6):905–913.
13. Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol*. 2006;49(3) 466-5; discussion 475.
14. Cookson MS, Chang SS, Oefelein MG, Gallagher JR, Schwartz B, Heap K. National practice patterns for immediate postoperative instillation of chemotherapy in nonmuscle invasive bladder cancer. *J Urol*. 2012;187(5):1571–1576.
15. Peyton CC, Chipollini J, Azizi M, Kamat AM, Gilbert SM, Spiess PE. Updates on the use of intravesical therapies for non-muscle invasive bladder cancer: how, when and what. *World J Urol*. 2019;37(10):2017–2029.
16. Bree KK, Shan Y, Hensley PJ, et al. Management, surveillance patterns, and costs associated with low-grade papillary stage Ta non-muscle-invasive bladder cancer among older adults, 2004-2013. *JAMA Netw Open*. 2022;5(3).
17. Alameddine M, Kineish O, Ritch C. Predicting Response to intravesical therapy in non-muscle-invasive bladder cancer. *Eur Urol Focus*. 2018;4(4):494–502.
18. Xylinas E, Kent M, Kluth L, et al. Accuracy of the EORTC risk tables and of the CUETO scoring model to predict outcomes in non-muscle-invasive urothelial carcinoma of the bladder. *Br J Cancer*. 2013;109(6):1460–1466.
19. Isharwal S, Konety B. Non-muscle invasive bladder cancer risk stratification. *Indian J Urol*. 2015;31(4):289–296.
20. Ravvaz K, Walz ME, Weissert JA, Downs TM. Predicting nonmuscle invasive bladder cancer recurrence and progression in a united states population. *J Urol*. 2017;198(4):824–831.
21. Wang T-W, Yuan H, Diao W-L, Yang R, Zhao X-Z, Guo H-Q. Comparison of gemcitabine and anthracycline antibiotics in prevention of superficial bladder cancer recurrence. *BMC Urol*. 2019;19(1):90.
22. Soukup V, Čapoun O, Cohen D, et al. Risk stratification tools and prognostic models in non-muscle-invasive bladder cancer: a critical assessment from the European Association of Urology Non-muscle-invasive Bladder Cancer Guidelines Panel. *Eur Urol Focus*. 2020;6(3):479–489.
23. Liu S, Hou J, Zhang H, et al. The evaluation of the risk factors for non-muscle invasive bladder cancer (NMIBC) recurrence after transurethral resection (TURBt) in Chinese population. *PLoS One*. 2015;10(4).
24. Garzotto M, Beer TM, Hudson RG, et al. Improved detection of prostate cancer using classification and regression tree analysis. *J Clin Oncol*. 2005;23(19):4322–4329.