

**Supplementary Figure 1. Oncologic outcomes of patients undergoing bladder-sparing treatment for BCG-unresponsive NMIBC, stratified by presence or absence of carcinoma *in situ* at time of BCG failure.** Kaplan-Meier curves showing recurrence-free (**A**), progression-free (**B**), cystectomy-free (**C**), and bladder-intact metastasis-free survival (**D**) of patients opting for initial bladder-sparing management of BCG-unresponsive NMIBC. Recurrence-free survival was a composite of high-grade intravesical and systemic recurrence. Progression-free survival was a composite of muscle-invasive (≥ T2) and metastatic (nodal/distant) progression. A large majority of patients experienced disease recurrence within the first two years, and over half underwent radical cystectomy within five years of initial BCG failure. Abbreviations: BCG, bacillus Calmette-Guérin; CIS, carcinoma *in situ*; NMIBC, non-muscle invasive bladder cancer.



**Supplementary Figure 2. Oncologic outcomes of patients undergoing initial cystectomy and 1 versus ≥ 2 lines of bladder-sparing treatment.** Kaplan-Meier curves showing metastasis-free (**A**) and cancer-specific (**B**) survival, stratified by receipt of initial RC, 1 line of BST, or ≥ 2 lines of BST. *p* values are per the log-rank test. Comparisons between groups should be made with caution given the likely presence of immortal-time bias in the ≥ 2 lines BST group. Abbreviations: BST, bladder-sparing treatment; RC, radical cystectomy.

| **Treatment** | ***n* (%)** |
| --- | --- |
| total patients | 89 |
| continued BCG (reinduction or additional maintenance) | 55 (62%) |
| alternate intravesical agents | 23 (26%) |
|  gemcitabine / docetaxel |  4 (4.5%) |
|  gemcitabine single agent |  11 (12%) |
|  mitomycin C |  3 (3.4%) |
|  other / clinical trial |  5 (5.6%) |
| re-TURBT or observation only | 9 (10%) |
| systemic pembrolizumab | 1 (1.1%) |
| non-standard regimen | 1 (1.1%) |

**Supplementary Table 1.** Bladder sparing treatments administered for BCG unresponsive non-muscle invasive bladder cancer. Only first-line treatments (i.e., administered at the point of BCG unresponsive disease) are included.

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Metastasis-free survival (univariable)** | **Metastasis-free survival (multivariable)** |
| **HR** | **95% CI** | ***p*** | **HR** | **95% CI** | ***p*** |
| treatment choice at BCG failure  |  |  |  |  |  |  |
|  radical cystectomy | reference |  |  |  |  |  |
|  bladder-sparing treatment | 1.31 | 0.68 - 2.52 | 0.42 |  |  |  |
| BCG failure modality |  |  |  |  |  |  |
|  ≥T1 disease after induction | reference |  |  | reference |  |  |
|  HG or ≥T1 ≤ 6 months after last maintenance | 0.67 | 0.32 - 1.39 | 0.28 | 0.80 | 0.33 - 1.90 | 0.61 |
|  CIS ≤ 12 months after last maintenance | 0.48 | 0.20 - 1.14 | 0.098 | 0.65 | 0.20 - 2.10 | 0.47 |
| year of BCG unresponsive diagnosis | 1.06 / year | 0.97 - 1.17 | 0.19 |  |  |  |
| age, years | 1.03 / year | 1.00 - 1.07 | 0.097 | 1.03 / year | 0.99 - 1.07 | 0.17 |
| female sex (vs male) | 0.89 | 0.39 - 2.04 | 0.78 |  |  |  |
| body mass index (BMI) (kg / m2) | 1.01 / point | 0.95 - 1.07 | 0.88 |  |  |  |
| Charlson comorbidity index | 1.12 / point | 0.94 - 1.35 | 0.21 |  |  |  |
| current or prior smoker (vs never smoker) | 1.14 | 0.56 - 2.30 | 0.72 |  |  |  |
| prior history of NMIBC (vs no history) | 0.71 | 0.31 - 1.62 | 0.42 |  |  |  |
| BCG at outside facility (versus at our facility) | 1.25 | 0.65 - 2.42 | 0.51 |  |  |  |
| initial tumor stage (prior to iBCG) |  |  |  |  |  |  |
|  Ta/Tis | reference |  |  |  |  |  |
|  T1 | 1.13 | 0.59 - 2.15 | 0.72 |  |  |  |
| presence of CIS prior to iBCG (versus no CIS) | 1.00 | 0.49 - 2.02 | 0.99 |  |  |  |
| tumor size at BCG failure |  |  |  |  |  |  |
|  small (< 2 cm) | reference |  |  | reference |  |  |
|  medium (2 - 5 cm) | 1.97 | 0.91 - 4.27 | 0.084 | 1.83 | 0.82 - 4.07 | 0.14 |
| tumor stage at BCG failure |  |  |  |  |  |  |
|  Ta/Tis | reference |  |  | reference |  |  |
|  T1 | 1.77 | 0.89 - 3.53 | 0.10 | 1.06 | 0.40 - 2.79 | 0.91 |
| presence of CIS at BCG failure (versus no CIS) | 0.91 | 0.46 - 1.81 | 0.80 |  |  |  |

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Cancer-specific survival (univariable)** | **Cancer-specific survival (multivariable)** |
| **HR** | **95% CI** | ***p*** | **HR** | **95% CI** | ***p*** |
| treatment choice at BCG failure  |  |  |  |  |  |  |
|  radical cystectomy | reference |  |  |  |  |  |
|  bladder-sparing treatment | 1.58 | 0.78 - 3.19 | 0.20 |  |  |  |
| BCG failure modality |  |  |  |  |  |  |
|  ≥T1 disease after induction | reference |  |  |  |  |  |
|  HG or ≥T1 ≤ 6 months after last maintenance | 0.91 | 0.42 - 1.98 | 0.81 |  |  |  |
|  CIS ≤ 12 months after last maintenance | 0.86 | 0.38 - 1.96 | 0.72 |  |  |  |
| year of BCG unresponsive diagnosis | 1.04 / year | 0.95 - 1.14 | 0.41 |  |  |  |
| age, years | 1.04 / year | 1.01 - 1.08 | 0.028 | 1.05 / year | 0.99 - 1.11 | 0.092 |
| female sex (vs male) | 0.55 | 0.20 - 1.57 | 0.27 |  |  |  |
| body mass index (BMI) (kg / m2) | 1.00 / point | 0.93 - 1.06 | 0.87 |  |  |  |
| Charlson comorbidity index | 1.25 / point | 1.03 - 1.50 | 0.023 | 1.01 / point | 0.83 - 1.46 | 0.51 |
| current or prior smoker (vs never smoker) | 2.42 | 0.93 - 5.40 | 0.072 | 2.47 | 0.93 - 6.54 | 0.069 |
| prior history of NMIBC (vs no history) | 1.27 | 0.61 - 2.65 | 0.52 |  |  |  |
| BCG at outside facility (versus at our facility) | 0.80 | 0.39 - 1.68 | 0.57 |  |  |  |
| initial tumor stage (prior to iBCG) |  |  |  |  |  |  |
|  Ta/Tis | reference |  |  |  |  |  |
|  T1 | 0.97 | 0.50 - 1.91 | 0.94 |  |  |  |
| presence of CIS prior to iBCG (versus no CIS) | 1.06 | 0.51 - 2.19 | 0.87 |  |  |  |
| tumor size at BCG failure |  |  |  |  |  |  |
|  small (< 2 cm) | reference |  |  | reference |  |  |
|  medium (2 - 5 cm) | 2.11 | 0.97 - 4.60 | 0.059 | 2.16 | 0.94 - 4.97 | 0.068 |
| tumor stage at BCG failure |  |  |  |  |  |  |
|  Ta/Tis | reference |  |  | reference |  |  |
|  T1 | 1.10 | 0.56 - 2.14 | 0.79 | 0.73 | 0.34 - 1.55 | 0.41 |
| presence of CIS at BCG failure (versus no CIS) | 0.84 | 0.42 - 1.70 | 0.63 |  |  |  |

**Supplementary Table 2.** Univariable and multivariable Cox regression analysis of factors associated with metastasis-free survival (top panel) and cancer-specific survival (bottom panel) in patients with BCG-unresponsive NMIBC. Covariates were selected for inclusion in the multivariable analysis based on a p value ≤ 0.10 on univariable analysis. Tumor grade is not shown because all tumors were high grade at initial presentation, and all but one tumor was high grade at the time of BCG-unresponsive disease. “Large” tumor size is excluded because all tumors were small or medium-sized at the time of BCG failure. Abbreviations: BCG, bacille Calmette-Guérin; BMI, body mass index; CI, confidence interval; HR, hazard ratio; LVI, lymphovascular invasion; NMIBC, non-muscle invasive bladder cancer.

| **Treatment** | **2nd line** | **3rd line** | **4th line** |
| --- | --- | --- | --- |
| additional BCG | 18 | 4 | 1 |
| gemcitabine single agent | 9 | 2 | 1 |
| gemcitabine/docetaxel | 4 | 5 | 1 |
| mitomycin C | 2 | 3 | 2 |
| systemic immune checkpoint inhibitor (e.g. pembrolizumab) | 2 | 1 | 2 |
| intravesical trial agent | 3 | 1 | 1 |
| valrubicin | 0 | 0 | 2 |
| chemoradiation (e.g. for progression to MIBC) | 2 | 0 | 0 |
| partial cystectomy | 0 | 1 | 0 |
| gemcitabine/mitomycin C | 0 | 0 | 0 |
| TOTAL | 40 | 17 | 10 |

**Supplementary Table 3.** Second- through fourth-line bladder-sparing treatment modalities in patients with failure of an initial course of bladder-sparing therapy. Abbreviations: BCG, bacillus Calmette-Guérin; MIBC, muscle invasive bladder cancer.

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Univariable** | **Multivariable** |
| **OR** | **95% CI** | ***p*** | **OR** | **95% CI** | ***p*** |
| BCG failure modality |  |  |  |  |  |  |
|  ≥T1 disease after induction | reference |  |  | reference |  |  |
|  HG or ≥T1 ≤ 6 months after last maintenance | 0.98 | 0.33 - 2.93 | 0.98 | 1.09 | 0.35 - 3.41 | 0.89 |
|  CIS ≤ 12 months after last maintenance | 0.18 | 0.04 - 0.89 | 0.036 | 0.18 | 0.04 - 0.91 | 0.038 |
| year of BCG unresponsive diagnosis | 1.07 / year | 0.94 - 1.20 | 0.31 |  |  |  |
| age, years | 0.99 / year | 0.95 - 1.04 | 0.67 |  |  |  |
| female sex (vs male) | 1.16 | 0.37 - 3.61 | 0.80 |  |  |  |
| body mass index (BMI) (kg / m2) | 0.71 / point | 0.39 - 1.31 | 0.27 |  |  |  |
| Charlson comorbidity index | 0.95 / point | 0.73 - 1.24 | 0.72 |  |  |  |
| current or prior smoker (vs never smoker) | 0.54 | 0.20 - 1.45 | 0.22 |  |  |  |
| prior history of NMIBC (vs no history) | 0.94 | 0.31 - 2.89 | 0.91 |  |  |  |
| BCG at outside facility (versus at our facility) | 0.64 | 0.24 - 1.72 | 0.38 |  |  |  |
| initial tumor stage (prior to iBCG) |  |  |  |  |  |  |
|  Ta/Tis | reference |  |  |  |  |  |
|  T1 | 1.89 | 0.70 - 5.12 | 0.21 |  |  |  |
| presence of CIS prior to iBCG (versus no CIS) | 0.53 | 0.17 - 1.66 | 0.28 |  |  |  |
| receipt of multiple lines of BST |  |  |  |  |  |  |
|  initial RC (0 lines BST) | reference |  |  | reference |  |  |
|  1 line BST | 1.26 | 0.35 - 4.60 | 0.73 | 1.51 | 0.39 - 5.77 | 0.55 |
|  2+ lines BST | 4.12 | 1.30 - 13.1 | 0.016 | 4.47 | 1.33 - 15.0 | 0.015 |
| tumor size at BCG failure |  |  |  |  |  |  |
|  small (< 2 cm) | reference |  |  |  |  |  |
|  medium (2 - 5 cm) | 0.94 | 0.24 - 3.73 | 0.93 |  |  |  |
| tumor stage at BCG failure |  |  |  |  |  |  |
|  Ta/Tis | reference |  |  |  |  |  |
|  T1 | 1.56 | 0.57 - 4.27 | 0.39 |  |  |  |
| presence of CIS at BCG failure (versus no CIS) | 0.66 | 0.24 - 1.84 | 0.43 |  |  |  |
| receipt of NACT (versus no NACT) |  |  |  |  |  |  |

**Supplementary Table 4.** Univariable logistic regression analysis of factors associated with pathologic extravesical disease (≥ pT3 or pN+) among patients undergoing radical cystectomy (either initial RC or following initial BST). Covariates were selected for inclusion in the multivariable analysis based on a p value ≤ 0.10 on univariable analysis. Tumor grade is not included because all tumors were high grade at initial presentation, and all but one tumor was high grade at the time of BCG-unresponsive disease. “Large” tumor size is excluded because all tumors were small or medium-sized at the time of BCG failure.

Abbreviations: BCG, bacille Calmette-Guérin; BMI, body mass index; BST, bladder-sparing treatment; CI, confidence interval; LVI, lymphovascular invasion; NACT, neoadjuvant chemotherapy; NMIBC, non-muscle invasive bladder cancer; OR, odds ratio; RC, radical cystectomy

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

|  |  |  |
| --- | --- | --- |
|  | Item No | Recommendation |
|  **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract - described in abstract |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found - provided in abstract |
| Introduction |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported - provided in Introduction |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses - last paragraph of Introduction |
| Methods |
| Study design | 4 | Present key elements of study design early in the paper - Patients and Methods section |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection - Patients section |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up - Patients and Data Collection sections |
| (*b*)For matched studies, give matching criteria and number of exposed and unexposed - N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable - Data Collection section |
| Data sources/ measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group - Data Collection and Statistical Methods sections |
| Bias | 9 | Describe any efforts to address potential sources of bias - study was not a comparison of two groups; standardized prespecified criteria were used in retrospective data collection to minimize bias as described in Data Collection. Bias was acknowleged in Limitations section. |
| Study size | 10 | Explain how the study size was arrived at - included all eligible patients available for analysis |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why - Data Collection section |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding - Statistical Methods section |
| (*b*) Describe any methods used to examine subgroups and interactions - N/A |
| (*c*) Explain how missing data were addressed - Statistical Methods |
| (*d*) If applicable, explain how loss to follow-up was addressed - proportion of LTFU was assessed and was low, as described in Results |
| (*e*) Describe any sensitivity analyses - N/A; publication is descriptive |
| Results |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed - Figure 1 (CONSORT diagram) |
| (b) Give reasons for non-participation at each stage - Figure 1 (CONSORT diagram) |
| (c) Consider use of a flow diagram - Figure 1 (CONSORT diagram) |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders - Table 1 |
| (b) Indicate number of participants with missing data for each variable of interest - as summarized in Table 1 |
| (c) Summarise follow-up time (eg, average and total amount) - Table 1 |
| Outcome data | 15\* | Report numbers of outcome events or summary measures over time - Figure 2, Figure 3, Table 2, Table 3, Table 4, Supplementary Figures 1-2 and Supplementary Table 2 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - Figure 2, Figure 3, Table 2, Table 3, Table 4, Supplementary Figures 1-2 and Supplementary Table 2 |
| (*b*) Report category boundaries when continuous variables were categorized - in all relevant tables |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period - absolute risk data provided in Table 2 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses - N/A |
| Discussion |
| Key results | 18 | Summarise key results with reference to study objectives - Discussion section |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias - Discussion and Limitations sections |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence - Discussion, Limitations, and Conclusions sections |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results - applicability and limitations reviewed in Discussion and Limitations sections |
| Other information |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based - no external funding |

\*Give information separately for exposed and unexposed groups.