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Risk of bladder cancer death in patients younger than 50 with non-muscle-invasive and muscle-invasive bladder cancer.

Running head:

Bladder cancer death in patients younger than 50

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1 **Abstract**

2 *Introduction and objectives*

3 Bladder cancer is primarily a disease of older age and little is known about the differences between
4 patients diagnosed with bladder cancer at a younger versus older age. Our objectives were to
5 compare bladder cancer specific survival in patients aged <50 versus those aged 50-70 at time of
6 diagnosis.

7 *Materials and Methods*

8 The Swedish bladder cancer database provided data on patient demographics, clinical
9 characteristics and treatments for this observational study. Cox proportional hazard regression
10 models were adjusted for appropriate variables. All analyses were stratified by disease stage (non-
11 muscle-invasive bladder cancer and muscle-invasive bladder cancer. Furthermore, we compared the
12 frequency of lower urinary tract infections within 24 months prior to bladder cancer diagnosis by sex
13 and age groups.

14 *Results*

15 The study included 15,452 newly-diagnosed BC patients (1997-2014); 1,207 (8%) patients were <50
16 whilst 14,245 (92%) were aged 50-70. Patients aged <50 at diagnosis were at a decreased risk of
17 bladder cancer death (HR=0.82, 95%CI: 0.68-0.99) compared to those aged 50-70. When stratified by
18 non-muscle-invasive and muscle-invasive bladder cancer, this association remained in non-muscle-
19 invasive patients only (<50, HR=0.43, 95% CI:0.28-0.64). The frequency of lower urinary tract
20 infection diagnoses did not differ between younger and older patients in either men or women.

21 *Conclusions*

22 Patients diagnosed with non-muscle-invasive bladder cancer when aged <50 are at decreased risk of
23 bladder cancer-specific death when compared to their older (50-70) counterparts. These

- 24 observations raise relevant research questions about age-related differences in diagnostic
- 25 procedures, clinical decision-making and, not least, potential differences in tumour biology.

26 **Introduction**

27 Bladder cancer (BC) is primarily a disease of older age with a median age at diagnosis of 74 in
28 Sweden [1]. Since the majority of BC patients are aged over 50, published literature naturally focuses
29 on older patients. Consequently, limited information is available on the demographics, clinical
30 characteristics, and survival outcomes for younger BC patients and how these compare to older
31 patients.

32

33 Recently, studies have attempted to answer such research questions; however, the majority have
34 been undertaken on single-centre or regional data and are therefore limited in their cohort sizes and
35 external validity [2–6]. To our knowledge, our study is the first European nationwide study
36 investigating clinical outcomes of young BC patients.

37

38 In this study, we aimed to compare the prognosis of BC patients aged <50, to those aged 50-70 in
39 terms of BC-specific death. Age 50 was the cut-off age as this is the age for commencing
40 standardized care pathways for individuals with macroscopic haematuria in Sweden, although also
41 younger individuals with macroscopic haematuria are referred to a urologist but outside
42 standardized care pathways due to a considerably lower risk of cancer [7]. We used 50-70 as the
43 main comparator since, within this age-span, general health in the majority of patients still permits
44 all treatments with curative intent, as in younger patients and in contrast to those patients in older
45 age-groups. This assumption is valid also for non-muscle invasive bladder cancer where age above 70
46 years is associated with independently higher risk of disease progression [8].

47 **Materials and Methods**

48 *Study Population and Variables*

49 The Bladder Cancer Data Base Sweden (BladderBaSe) was created in 2015. It links information from
50 the Swedish National Register of Urinary Bladder Cancer (SNRUBC) from 1997 to 2014, with a
51 number of national health care and demographic registers through personal identification numbers
52 [9,10]. The research was approved by the Research Ethics Board of Uppsala University, Sweden (File
53 no. 2015/277).

54

55 In Sweden a National Board of Health and Welfare consensus from 1999 recommended that
56 microhaematuria testing in adults should be abandoned [11], and primary care physicians refer only
57 individuals with macroscopic haematuria or those with urinary tract symptoms and microscopic
58 haematuria. Thus, the proportion of patients diagnosed with bladder cancer based on microscopic
59 haematuria has been below 4% in Swedish population-based series [12], although information about
60 reasons behind referrals are lacking in the current study.

61

62 All patients diagnosed with BC (any T, any N, any M) between January 1st 1997 and December 31st
63 2014 were included. Data on the patients' demographics and clinical characteristics were extracted:
64 age, sex, education (low (≤ 9 years of school), intermediate (10–12 years), high (≥ 13 years)), civil
65 status (unmarried, married, widowed, divorced), Charlson Comorbidity Index (CCI) (0, 1, 2, 3+),
66 clinical TNM stage, tumour grade (WHO 1973 (1997–2002) and WHO 1999 (2003 onwards)). Patients
67 with missing age or clinical T stage were excluded. Information was extracted regarding patients'
68 treatments at diagnosis. To adjust for possible confounding by LUTIs, we obtained information for
69 ICD-10 codes N30 (cystitis), N30.9 (cystitis unspecified), N34 (urethritis) and N39 (disorder of urinary
70 system caused by infection with unspecified location). NMIBC patients were stratified as low/high
71 risk. Low risk NMIBC was defined as TaG1-G2, whilst high risk was defined as any of TaG3/Tis/T1.

72 MIBC patients were also stratified by non-metastatic vs. metastatic. Treatments for MIBC patients
73 with N+ disease were analysed separately.

74

75 *Statistical Analyses*

76 Descriptive analyses were undertaken for demographic and clinical information and stratified by age
77 groups (<50 and 50-70). Chi-squared tests were used to identify differences between demographic
78 and clinical characteristics for the age groups. To refine the Chi-squared significance, tests of
79 proportions were subsequently performed on those variables identified as varying between age
80 groups.

81

82 Using age <50 as the exposure of interest, Cox proportional hazards regression models were
83 performed to calculate hazard ratios (HRs) as a measure of relative risk of BC death. All analyses
84 were adjusted for sex, CCI, civil status, education, tumour grade and clinical (c)TNM stage.

85 Adjustments were determined through the use of a directed acyclic graph using the DAGitty tool
86 [13]. We additionally adjusted for the number of LUTIs diagnosed in the two years prior to BC
87 diagnosis. Furthermore, two sensitivity analyses were performed: 1) age ≤ 40 was used as the
88 exposure, and 2) exclusion of patients with M+ and N+ disease.

89

90 All data analysis was performed using STATA 16.1 (Texas, USA).

91 **Results**

92 *Cohort Characteristics*

93 We identified 15,452 patients in BladderBaSe: 1,207 (8%) were aged <50; 14,245 (92%) aged 50-70.

94 **Table 1** summarizes the cohort demographics. The age groups differed in sex distribution with a
95 higher proportion of females in the 50-70 age group than the younger age group. The <50 group had
96 a higher proportion of cTa patients compared to the 50-70s; there was also a higher frequency of G1
97 tumours in the <50 group. A higher proportion of patients in the <50 had a CCI of 0 (90%) compared
98 to the 50-70s. The cohort demographics showed a similar pattern of distribution when stratified by
99 sex (Supplementary Table 1). Furthermore, there was an even distribution of patients within each
100 age group across the study time-frame from 1997 to 2014.

101

102 Six percent (n=902) of patients experienced a LUTI during the two years prior to their BC diagnosis.

103 When stratified by age, 5% of patients aged <50 had experienced 1-2 LUTIs, compared to 6% in the
104 50-70s. Across all age groups, the proportion of women experiencing at least one LUTI in the two
105 years prior to BC diagnosis was statistically significantly larger than for men (8% vs. 5%, p<0.0294).

106

107 *Treatments – NMIBC*

108 Of all NMIBC patients, 8% (aged<50) and 12% (50-70) of patients had received intravesical
109 treatment. Four percent of low risk NMIBC patients aged <50 received intravesical therapy with
110 serial instillations, compared to 5% of patients age 50-70 (**Table 2**). In the high risk group, 20% of
111 patients aged <50 received intravesical therapy with serial instillations compared to 26% of patients
112 aged 50-70. Four percent of NMIBC patients had received a single-dose of post-operative
113 chemotherapy with similar proportions observed between the age groups. In those with high-risk
114 NMIBC, 13% aged <50 underwent radical cystectomy compared to 10% aged 50-70.

115

116 With respect to external-beam radiotherapy in the non-metastatic MIBC patients, three (2%)
117 patients aged <50 received such treatment compared to 105 (4%) patients aged 50-70 (**Table 2**).
118 Sixty-eight percent of non-metastatic MIBC patients underwent radical cystectomy (77% in those
119 aged <50 and 67% in those aged 50-70). The proportion of non-metastatic MIBC patients who
120 received neoadjuvant chemotherapy (NAC) in conjunction with radical cystectomy was 15% in those
121 aged <50 and 12% in those aged 50-70. When the use of NAC was assessed over time in the non-
122 metastatic MIBC patients, there was a steady increase in usage of NAC across age groups (1997-
123 2014) (Supplementary Figure 1).

124
125 The proportion of patients with metastatic disease (N+/M1) on best supportive care was lowest in
126 those aged <50 (20%) compared to those aged 50-70 (38%) (Table 2). When the MIBC N+ patients
127 were analysed separately, similar proportions of patients underwent radical cystectomy and
128 perioperative chemotherapy among the <50 and 50-70s (47% vs 49% and 21% vs 21% respectively).

129

130 *Risk of bladder cancer death*

131 Overall median follow-up was 5.30 years (IQR:1.92-10.14). Patients aged <50 at diagnosis were at a
132 decreased risk of BC death (HR=0.82, 95%CI: 0.68-0.99) compared to those aged 50-70 (**Table 3**).
133 When survival analyses were adjusted for number of LUTI diagnoses in the two years prior to
134 diagnosis, the results remained unchanged.

135

136 *Risk of bladder cancer death – NMIBC*

137 In the NMIBC patients, those aged <50 at diagnosis were at a decreased risk of BC death (HR=0.43,
138 95%CI:0.28-0.64) compared to those aged 50-70 (Table 3). Kaplan Meier analyses also showed
139 similar associations, including when stratified by sex (**Figures 1 and 2** and supplementary Figures 2
140 and 3). The 5- and 10-year survival proportions were 98% and 96% for those aged <50, and 95% and
141 92% in those aged 50-70 (Table 4). The same pattern of associations remained when the NMIBC

142 patients were stratified by low and high risk patients, and when adjusted for number of LUTI
143 diagnoses in the two years prior to diagnosis.

144

145 When considering patients aged <40 in the younger group, the results were no longer statistically
146 significant for all NMIBC and when stratified by low and high risk NMIBC (Table 3). Furthermore,
147 when excluding patients with N+/M+ disease from analyses, the results were no longer statistically
148 significant for high-risk NMIBC. Other sensitivity analyses did not statistically significantly alter the
149 results for NMIBC patients.

150

151 *Risk of bladder cancer death - MIBC*

152 For MIBC patients, the risk of death in the <50 group did not differ to those aged 50-70 (HR=0.99,
153 95%CI:0.79-1.23) (Table 3). We found the same pattern of association when MIBC patients were
154 stratified by non-metastatic and metastatic patients, and when adjusted for number of LUTI
155 diagnoses in the two years prior to diagnosis. The sensitivity analyses did not statistically significantly
156 alter any of the results for the MIBC patients.

157 **Discussion**

158 In this nationwide observational study, BC patients diagnosed aged <50 had a statistically
159 significantly decreased risk of BC-specific death when compared to patients aged 50-70. When
160 stratified by stage, this association remained in patients with NMIBC, both low and high risk. In those
161 with MIBC, the risk of BC-specific death did not differ between age categories.

162

163 Previous studies have investigated clinical outcomes for younger BC patients although, to our
164 knowledge, this is the first study using population-based national data. With respect to risk of death,
165 a study by Lara et al [3] concluded that younger patients had a 58% reduced risk of BC death
166 ($p < 0.001$) compared to older patients. These results are in-line with the results from our study,
167 although we only observed reduced risk in NMIBC patients. The study by Lara et al, however, did not
168 stratify their analysis by T stage. Furthermore, the lack of information on cisplatin-eligibility in that
169 and the present study diminishes the possibility to further disentangle survival differences in
170 younger patients with MIBC [14]. Cisplatin-based chemotherapy constitutes a guideline-driven and
171 integral part of MIBC treatment in all eligible patients [15]; however, above 70 years of age the
172 proportion of patients eligible for cisplatin decreases largely due to impaired renal function [16].

173

174 We identified different associations for age-related risk of death between NMIBC and MIBC patients.
175 Janisch et al conducted a study in MIBC patients treated with radical cystectomy and reported a null
176 association between age <50 vs. >50 and risk of cancer specific death [4]. The study by Feng et al
177 also investigated the effect of age on risk of death stratified by tumour stage and reported a longer
178 survival time (BC-specific) for those aged <50 for all stages, thereby diverging from the current
179 results [17]. In our study, the <50s had the highest proportion of patients with Ta tumours, whilst
180 the 50-70s had the highest proportion of patients with invasive tumours, especially stages T1-2.
181 However, the proportion of T3-T4, as well as metastatic patients (M+/N+), did not differ greatly
182 between the age groups. Therefore, one possible explanation behind the observed association is

183 that there is a disease stage cut-off (representing local tumour biology and metastatic potential)
184 beyond which the benefits of youth are negated. A study by Tian et al. [18] concluded that younger
185 MIBC patients were at increased risk of locoregional lymph node metastasis compared to their older
186 counterparts in a selected population treated with radical cystectomy and lymphadenectomy (where
187 at least one lymph node was examined). In the present study we have utilised clinical lymph node
188 staging, rather than the number of positive excised lymph nodes at cystectomy.

189

190 Since patients with higher stage grade have higher mortality [19], the statistically significant
191 difference between stages and grades between the age groups may in part explain the differences in
192 BC-specific mortality risk observed - in the current study the <50s had more cTa and low grade
193 tumours compared to their older counterparts, as also reported (for grade) by both de la Calle et al
194 [5] and Telli et al [20]. These differences in stages and grades may suggest different disease biology
195 between the age groups; hence, investigating the distribution of taxonomic subgroups is of merit for
196 further future research, similar to that of Shelekhova et al [21]. Here the authors concluded that
197 more aggressive molecular subtypes were more frequent in older patients. Similarly, the basal-
198 squamous like subtype has been associated with higher age [22]. The molecular pathobiology of BC
199 is complex [23], however, it is feasible to consider that, in the absence of age-related
200 immunosenescence [24], younger patients may be better able to corral transformed cells within the
201 urothelium and limit migration beyond the basal membrane. Equally, symptom-related health-
202 seeking behaviour may differ between age groups and this may be reflected subsequently by the
203 observed differences in stages at diagnosis. Furthermore, the allocation of perioperative
204 chemotherapy for non-metastatic patients differed between age groups (higher proportion aged <50
205 receiving such treatments than those aged 50-70). It is also worth mentioning that there were some
206 regional differences in treatment allocation. For example, there appeared to be a higher proportion
207 of younger patients who received intravesical therapy in the South when compared to the
208 background population of NMIBC in that region (37% vs. 21%). Meanwhile, in Stockholm and

209 Uppsala, the proportion of young patients receiving intravesical therapy appears to be smaller than
210 the background population (10% vs. 22% and 9% vs. 17% respectively).

211

212 There is heterogeneity in how to define 'younger patients' in the existing literature, with <40 used
213 elsewhere [3,5]. Our sensitivity analyses did however change the statistical significance of the results
214 for NMIBC patients albeit with lower numbers (n=296) than in previous studies by Lara et al
215 (n=1,688) [3] and de la Calle et al (n=3,314) [5]. Since the presence of gross haematuria in ≥50s
216 triggers standardized care pathways in Sweden, we considered this as an appropriate cut-off for this
217 dataset.

218

219 The occurrence of LUTIs before diagnosis did not confound the comparison between those <50 with
220 those 50-70. As a higher proportion of women than men are diagnosed with LUTI prior to BC
221 diagnosis, and women also are diagnosed with BC at a later stage [25], further study is warranted of
222 the association between LUTI and misinterpretation of symptoms and delayed diagnosis [26–28].
223 However, to investigate how the age and sex distribution noted in our study compare to the one
224 expected in a background non-BC population, controls would be necessary. Controls will be added to
225 the next version of BladderBaSe hence making such a study possible in the future.

226

227 The strengths of this study include the use of data from the BladderBaSe for over 15,000 newly-
228 diagnosed BC cases in Sweden with the possibility to stratify by age groups and by NMIBC and MIBC.
229 Furthermore, linkage of the BladderBaSe to both inpatient and outpatient registers permitted
230 analysis of LUTI diagnoses during the two years prior to BC diagnosis. Limitations include missingness
231 of some variables such as N stages (65% were either NX or missing) related to the lack of cross-
232 sectional imaging in patients with a low risk of lymph node metastases or substantial comorbidity
233 (where presence of lymph node metastases would not alter the treatment plan). Therefore, we were
234 not able to confirm or refute the results from the Chi-squared test for this variable [18]. We also did

235 not have access to any data regarding tobacco smoking or occupation therefore were not able to
236 study or adjust for these variables within our analyses. There is also difficulty in separating the
237 clinical stages T2 and T3 in routine practice, though here we only report descriptive data and do not
238 make any firm conclusions based on clinical stage. For LUTIs, the patients captured may have
239 encompassed the most severe infections and may not be representative of all LUTIs or upper tract
240 UTIs related to ureteric obstruction by yet-to-be-diagnosed BC. We also note that, for all stages and
241 age groups, there appears to be low utilisation of adjuvant peri-operative therapies (both
242 intravesical and systemic) which may limit the generalisability of our findings.

243

244 **Conclusion**

245 This study has demonstrated a decreased risk of BC death in patients who are diagnosed with NMIBC
246 aged <50 when compared to those diagnosed at age 50-70. The distribution of stage and grade
247 among these younger patients may in part explain these differences as well as possible differences in
248 tumour biology associated with onset of disease in different age groups either as result of, or in
249 parallel with, diagnostic biases, treatment allocations, and differences. It is also possible that the
250 change in behaviours over the years with habits such as tobacco smoking may have influenced these
251 results. These observations raise relevant research questions regarding age-related differences in
252 diagnostic delay, clinical decision-making, and tumour biology.

253

254

255

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262 Fredrik Liedberg, and Staffan Jahnson.

263

264 **Conflicts of Interest**

265 There are no conflicts of interest to declare.

266

267 **Ethics**

268 Research was approved by the Research Ethics Board of Uppsala University, Sweden (File no.
269 2015/277).

270

271 **Data availability**

272 The BladderBaSe data is held on a secure server and is therefore not publicly available. However,
273 applications to access the data can be made by contacting support.rc-norr@vll.se.

274

275 **Author contributions statement**

276 Study design – All authors. Data analysis – BR, OH, FL, LH, MVH. Writing and review of the
277 manuscript – All authors.

278 **References**

- 279 1. Swedish National Quality Register for Bladder and Urinary Tract Cancer (SNRUBC) [Internet].
280 2019. Available from: <https://statistik.incanet.se/Urinblasecancer/>
- 281 2. Katafigiotis I, Sfoungaristos S, Martini A, et al. Bladder Cancer to Patients Younger than 30
282 Years: A Retrospective Study and Review of the Literature. *Urol J* [Internet]. 2017 Oct 9 [cited
283 2019 Aug 13];84(4):231–5. Available from:
284 <http://journals.sagepub.com/doi/10.5301/uj.5000264>
- 285 3. Lara J, Brunson A, Keegan TH., et al. Determinants of survival in adolescents and young adults
286 with urothelial bladder cancer: results from the California Cancer Registry. *J Urol*.
287 2016;196(5):1378–82.
- 288 4. Janisch F, Yu H, Vetterlein MW, et al. Do Younger Patients with Muscle-Invasive Bladder
289 Cancer have Better Outcomes? *J Clin Med*. 2019;8(9):1–10.
- 290 5. de la Calle CM, Washington SL, Lonergan PE, et al. Bladder cancer in patients younger than
291 40 years: outcomes from the National Cancer Database. *World J Urol* [Internet].
292 2020;(0123456789). Available from: <https://doi.org/10.1007/s00345-020-03376-9>
- 293 6. Wang ZH, Li YY, Hu ZQ, et al. Does urothelial cancer of bladder behave differently in young
294 patients? *Chin Med J (Engl)*. 2012;125(15):2643–8.
- 295 7. Nilbert M, Bläckberg M, Ceberg J, et al. Diagnostic pathway efficacy for urinary tract cancer:
296 population-based outcome of standardized evaluation for macroscopic haematuria. *Scand J*
297 *Urol* [Internet]. 2018 Jul 4 [cited 2019 Jan 14];52(4):237–43. Available from:
298 <https://www.tandfonline.com/doi/full/10.1080/21681805.2018.1498124>
- 299 8. Sylvester RJ, Rodríguez O, Hernández V, et al. European Association of Urology (EAU)
300 Prognostic Factor Risk Groups for Non–muscle-invasive Bladder Cancer (NMIBC)
301 Incorporating the WHO 2004/2016 and WHO 1973 Classification Systems for Grade: An

- 302 Update from the EAU NMIBC Guidelines Panel[Formula presented]. *Eur Urol.* 2021;79(4):480–
303 8.
- 304 9. Haggstrom C, Liedberg F, Hagberg O, et al. Cohort profile: The Swedish National Register of
305 Urinary Bladder Cancer (SNRUBC) and the Bladder Cancer Database Sweden (BladderBaSe).
306 *BMJ Open.* 2017;7(9):e016606.
- 307 10. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity
308 number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*
309 [Internet]. 2009 [cited 2017 Sep 28];24:659–67. Available from:
310 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2773709/pdf/10654_2009_Article_9350.pdf
- 311 11. Malmström PU. Time to abandon testing for microscopic haematuria in adults? *Br Med J.*
312 2003;326(7393):813–5.
- 313 12. Månsson Å, Anderson H, Colleen S. Time lag to diagnosis of bladder cancer-influence of
314 psychosocial parameters and level of health-care provision. *Scand J Urol Nephrol.*
315 1993;27(3):363–9.
- 316 13. Textor J, van der Zander B, Gilthorpe MK, et al. Robust causal inference using directed acyclic
317 graphs: the R package “dagitty”. *Int J Epidemiol* [Internet]. 2016;45(6):1887–94. Available
318 from: <http://www.dagitty.net/>
- 319 14. Jiang DM, Gupta S, Kitchlu AK, et al. Defining cisplatin eligibility in patients with muscle-
320 invasive bladder cancer. *Nat Rev Urol* [Internet]. 2021; Available from:
321 <http://dx.doi.org/10.1038/s41585-020-00404-6>
- 322 15. Witjes JA, Bruins HM, Cathomas R, et al. European Association of Urology Guidelines on
323 Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines [Internet].
324 Vol. 79, *European Urology.* Elsevier B.V.; 2021 [cited 2021 Feb 25]. p. 82–104. Available from:
325 <https://doi.org/10.1016/j.eururo.2020.03.055>

- 326 16. Canter D, Viterbo R, Kutikov A, et al. Baseline renal function status limits patient eligibility to
327 receive perioperative chemotherapy for invasive bladder cancer and is minimally affected by
328 radical cystectomy. *Urology* [Internet]. 2011 Jan 1 [cited 2021 Feb 26];77(1):160–5. Available
329 from: <http://www.goldjournal.net/article/S0090429510006588/fulltext>
- 330 17. Feng H, Zhang W, Li J, et al. Different patterns in the prognostic value of age for bladder
331 cancer-specific survival depending on tumor stages. *Am J Cancer Res*. 2015;5(6):2090–7.
- 332 18. Tian Z, Meng L, Wang X, et al. Young age increases the risk of lymph-node metastasis in
333 patients with muscle-invasive bladder urothelial carcinoma. *BMC Cancer*. 2020;20(1):1–6.
- 334 19. Kirkali Z, Chan T, Manoharan M, et al. Bladder Cancer: Epidemiology, staging and grading, and
335 diagnosis. *Urology* [Internet]. 2005 [cited 2018 Apr 12];66:4–34. Available from:
336 [http://www.goldjournal.net/article/S0090-4295\(05\)01490-1/pdf](http://www.goldjournal.net/article/S0090-4295(05)01490-1/pdf)
- 337 20. Telli O, Sarici H, Ozgur BC, et al. Urothelial cancer of Bladder in young versus older adults:
338 Clinical and pathological characteristics and outcomes. *Kaohsiung J Med Sci*. 2014;30(9):466–
339 70.
- 340 21. Shelekhova K V., Krykow KA, Mescherjakov IA, et al. Molecular Pathologic Subtyping of
341 Urothelial Bladder Carcinoma in Young Patients. *Int J Surg Pathol*. 2019;27(5):483–91.
- 342 22. Sun X, Hoadley KA, Kim WY, et al. Age at diagnosis, obesity, smoking, and molecular subtypes
343 in muscle-invasive bladder cancer. *Cancer Causes Control* [Internet]. 2017 Jun 1 [cited 2021
344 Feb 25];28(6):539–44. Available from: <https://pubmed.ncbi.nlm.nih.gov/28321693/>
- 345 23. Ward DG, Arnold R, Bryan RT. Molecular Subtypes of T1 Bladder Cancer: Biomolecular
346 Characteristics Versus Clinical Utility [Internet]. Vol. 78, *European Urology*. Elsevier B.V.; 2020
347 [cited 2021 Feb 25]. p. 538–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/32773351/>
- 348 24. Lian J, Yue Y, Yu W, et al. Immunosenescence: a key player in cancer development [Internet].
349 Vol. 13, *Journal of Hematology and Oncology*. BioMed Central Ltd; 2020 [cited 2021 Feb 25].

350 Available from: <https://pubmed.ncbi.nlm.nih.gov/33168037/>

351 25. Andreassen BK, Grimsrud TK, Haug ES. Bladder cancer survival: Women better off in the long
352 run. *Eur J Cancer* [Internet]. 2018;95:52–8. Available from:
353 <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=296351>
354 44

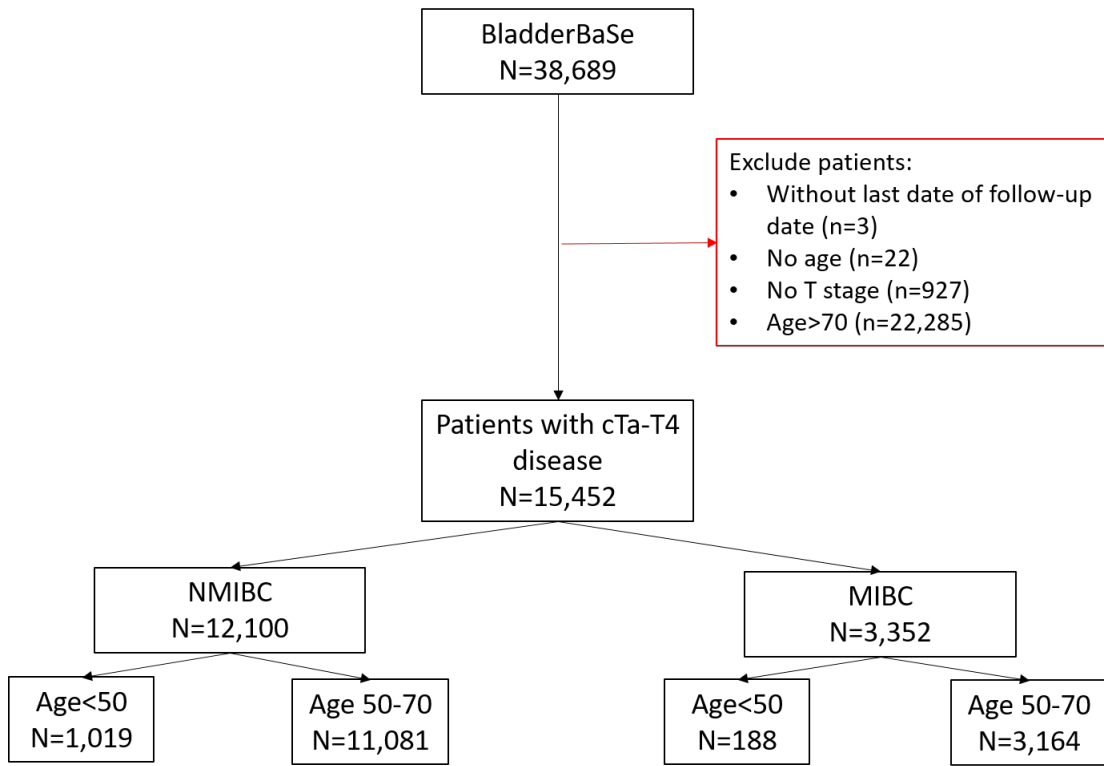
355 26. Cumberbatch MGK, Jubber I, Black PC, et al. Epidemiology of Bladder Cancer: A Systematic
356 Review and Contemporary Update of Risk Factors in 2018. *Eur Urol* [Internet].
357 2018;74(6):784–95. Available from: <https://doi.org/10.1016/j.eururo.2018.09.001>

358 27. Bryan RT, Evans T, Dunn JA, et al. A Comparative Analysis of the Influence of Gender, Pathway
359 Delays, and Risk Factor Exposures on the Long-term Outcomes of Bladder Cancer. *Eur Urol*
360 *Focus* [Internet]. 2015;1:82–9. Available from: <http://dx.doi.org/10.1016/j.euf.2015.01.001>

361 28. Foxman B. Urinary tract infection in postmenopausal women. *Curr Infect Dis Rep*.
362 1999;1:367–70.

363

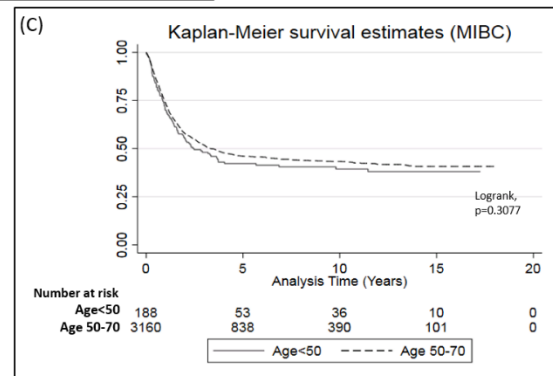
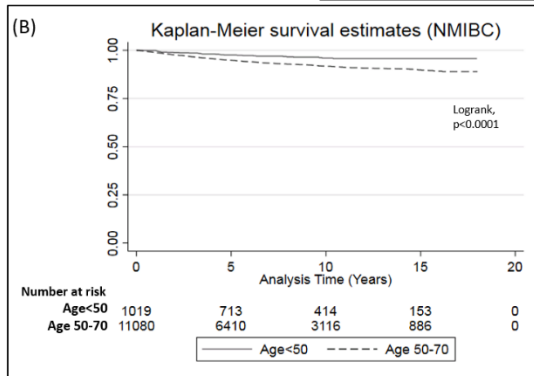
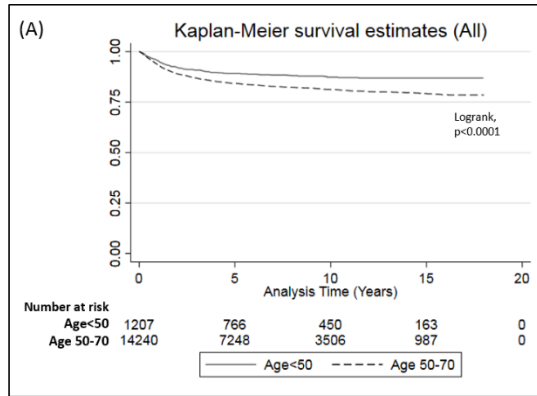
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367 **Figure 1.** Cohort selection process

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369

370 **Figure 2.** Kaplan Meier curves for bladder cancer specific survival when stratified by age group (<50
 371 vs 50-70). (A) All patients, (B) Non-muscle invasive bladder cancer patients (NMIBC) and (C) Muscle
 372 invasive bladder cancer patients (MIBC).

373

374 **Table 1. Cohort Demographics when stratified by age groups.**

Variable	Total		Age <50		Age 50-70		P value
	n=15,452		n=1,207		n=14,245		
	N	%	N	%	N	%	
Sex							
Male	3,784	24.50	331	27.40	3,453	24.20	0.014
Female	11,668	75.50	876	72.60	10,792	75.80	
BC Type							
NMIBC	12,100	78.30	1,019	84.40	11,081	77.80	<0.0001
MIBC	3,352	21.70	188	15.60	3,164	22.20	
Clinical T stage							
Ta	8,369	54.20	795	65.90	7,574	53.20	<0.0001
Tis	461	3.00	17	1.40	444	3.10	
T1	3,270	21.20	207	17.10	3,063	21.50	
T2	2,223	14.40	104	8.60	2,119	14.90	
T3	683	4.40	47	3.90	636	4.50	
T4	446	2.90	37	3.10	409	2.90	
Clinical N stage							
N0	4,804	31.10	333	27.60	4,471	31.40	0.019
N+	622	4.00	55	4.60	567	4.00	
NX	9,946	64.40	809	67.00	9,137	64.10	
Missing	80	0.50	10	0.80	70	0.50	
Clinical M stage							
M0	4,737	30.70	331	27.40	4,406	30.90	0.034
M1	426	2.80	27	2.20	399	2.80	
MX	10,139	65.60	838	69.40	9,301	65.30	
Missing	150	1.00	11	0.90	139	1.00	
Tumour Grade							
G1	4,533	29.30	480	39.80	4,053	28.50	<0.0001
G2	4,873	31.50	346	28.70	4,527	31.80	
G3	5,208	33.70	275	22.80	4,933	34.60	
G4	87	0.60	10	0.80	77	0.50	
GX	190	1.20	14	1.20	176	1.20	
Missing	561	3.60	82	6.80	479	3.40	
Civil Status							
Unmarried	2,408	15.60	500	41.40	1,908	13.40	<0.0001
Married	9,505	61.50	493	40.80	9,012	63.30	
Divorced	2,651	17.20	131	10.90	2,520	17.70	
Widowed	591	3.80	5	0.40	586	4.10	
Missing	297	1.90	78	6.50	219	1.50	
Education							
Low	5,412	35.00	231	19.10	5,181	36.40	<0.0001

Medium	6,439	41.70	601	49.80	5,838	41.00	
High	3,403	22.00	363	30.10	3,040	21.30	
Missing	198	1.30	12	1.00	186	1.30	
CCI							
0	11,145	72.10	1,089	90.20	10,056	70.60	<0.0001
1	1,904	12.30	49	4.10	1,855	13.00	
2	1,447	9.40	46	3.80	1,401	9.80	
3+	956	6.20	23	1.90	933	6.50	

375 CCI – Charlson Comorbidity Index; NMIBC – non-muscle invasive bladder cancer; MIBC – muscle
376 invasive bladder cancer

Table 2 – Treatment types when stratified by age groups and NMIBC (low and high risk) and MIBC (non-metastatic and metastatic).

Patients	Treatment	Total		Age <50		Age 50-70	
		N	%	N	%	N	%
Low risk NMIBC (TaG1-G2)		n=7,434		n=697		n=6,737	
	Intravesical treatment (BCG or chemotherapy)	354	4.8	30	4.3	324	4.8
	Single-dose chemotherapy	352	4.7	30	4.3	322	4.8
	Radical cystectomy	31	0.4	4	0.6	27	0.4
	Re-resection	307	4.1	20	2.9	287	4.3
High risk NMIBC (TaG3/Tis/T1)		n=4,273		n=251		n=4,022	
	Intravesical treatment (BCG or chemotherapy)	1,093	25.6	51	20.3	1,042	25.9
	Single-dose chemotherapy	166	3.9	6	2.4	160	4.0
	Radical cystectomy	443	10.4	32	12.7	411	10.2
	Re-resection	922	21.6	50	19.9	872	21.7
Non-metastatic MIBC		n=2,546		n=131		n=2,415	
	External beam radiotherapy	108	4.2	3	2.3	105	4.3
	Systemic chemotherapy	560	22.0	40	30.5	520	21.5
	Radical cystectomy	1,724	67.7	101	77.1	1,623	67.2
	NAC	301	11.8	20	15.3	281	11.6

	Adjuvant chemotherapy	122	4.8	14	10.7	108	4.5
	Urinary Diversion type	n=1,724		n=101		n=1,623	
	Bladder substitution	404	23.4	36	35.6	368	22.7
	Continent cutaneous	206	11.9	20	19.8	186	11.5
	Non-continent	1,094	63.5	42	41.6	1,052	64.8
	Missing	20	1.2	3	3.0	17	1.0
		n=763		n=54		n=709	
Metastatic MIBC (N+/M1)	External beam radiotherapy	18	2.4	1	1.9	17	2.4
	Systemic chemotherapy	323	42.3	33	61.1	290	40.9
	Radical cystectomy	298	39.1	23	42.6	275	38.8
	Adjuvant chemotherapy	71	9.3	4	7.4	67	9.4
	Best supportive care	281	36.8	11	20.4	270	38.1
			n=552		n=47		n=505
MIBC N+ only	Systemic chemotherapy	252	45.7	29	61.7	223	44.2
	Radical cystectomy	268	48.6	22	46.8	246	48.7
	NAC/Induction Chemotherapy	51	9.2	6	12.8	45	8.9
	Adjuvant chemotherapy	67	12.1	4	8.5	63	12.5

NMIBC – non-muscle invasive bladder cancer; MIBC – muscle invasive bladder cancer; BCG – Bacillus Calmette-Guerin; NAC – neoadjuvant chemotherapy

Table 3 – Hazard ratios (HR) and 95% confidence intervals (CIs) for risk of bladder cancer death.

Patients		Variable	HR	95% CI	HR ^a	95%CI
All	Age	<50	0.64	(0.54-0.77)	0.82	(0.68-0.99)
		50-70	1.00	Ref.	1.00	Ref.
	Sensitivity Analyses	<40	0.38	(0.24-0.59)	0.69	(0.42-1.12)
		40-70	1.00	Ref.	1.00	Ref.
	Excl. N+/M+	<50	0.58	(0.47-0.71)	0.82	(0.65-1.03)
		50-70	1.00	Ref.	1.00	Ref.
NMIBC	Age	<50	0.43	(0.30-0.62)	0.43	(0.28-0.64)
		50-70	1.00	Ref.	1.00	Ref.
	Sensitivity Analyses	<40	0.23	(0.09-0.61)	0.38	(0.14-1.03)
		40-70	1.00	Ref.	1.00	Ref.
	Excl. N+/M+	<50	0.44	(0.32-0.62)	0.56	(0.38-0.81)
		50-70	1.00	Ref.	1.00	Ref.
TaG1-2	Age	<50	0.22	(0.09-0.54)	0.28	(0.11-0.70)
		50-70	1.00	Ref.	1.00	Ref.
	Sensitivity Analyses	<40	0.18	(0.02-1.25)	0.26	(0.04-1.92)
		40-70	1.00	Ref.	1.00	Ref.
	Excl. N+/M+	<50	0.23	(0.10-0.53)	0.30	(0.13-0.68)
		50-70	1.00	Ref.	1.00	Ref.
TaG3/Tis/T1	Age	<50	0.70	(0.47-1.05)	0.49	(0.31-0.78)
		50-70	1.00	Ref.	1.00	Ref.
	Sensitivity Analyses	<40	0.47	(0.15-1.47)	0.44	(0.14-1.41)
		40-70	1.00	Ref.	1.00	Ref.
	Excl. N+/M+	<50	0.73	(0.50-1.07)	0.72	(0.47-1.09)
		50-70	1.00	Ref.	1.00	Ref.
MIBC	Age	<50	1.11	(0.91-1.36)	0.99	(0.79-1.23)
		50-70	1.00	Ref.	1.00	Ref.
	Sensitivity Analyses	<40	1.01	(0.61-1.68)	0.92	(0.52-1.61)
		40-70	1.00	Ref.	1.00	Ref.
MIBC non-metastatic	Age	<50	1.07	(0.83-1.38)	1.01	(0.77-1.34)
		50-70	1.00	Ref.	1.00	Ref.
	Sensitivity Analyses	<40	0.96	(0.50-1.85)	0.73	(0.35-1.54)
		40-70	1.00	Ref.	1.00	Ref.
MIBC metastatic	Age	<50	1.01	(0.73-1.40)	0.91	(0.62-1.34)
		50-70	1.00	Ref.	1.00	Ref.
	Sensitivity Analyses	<40	1.20	(0.54-2.69)	1.16	(0.46-2.88)
		40-70	1.00	Ref.	1.00	Ref.

Sensitivity analyses consist of using ≤ 40 as the exposure variable and excluding all patients with N+ or M+ disease. NMIBC – non-muscle invasive bladder cancer; MIBC – muscle invasive bladder cancer. HR – unadjusted HR; HR^a- Adjusted HR

Table 4 – 5 and 10-year survival proportions and 95% confidence intervals when stratified by age groups

	Cohort	5 year (%)	95% CI (%)	10 year (%)	95% CI (%)
All	All	84.7	(84.0-85.3)	81.8	(81.1-82.5)
	<50	89.2	(87.1-90.9)	87.4	(85.1-89.3)
	50-70	84.3	(83.6-84.9)	81.3	(80.5-82.0)
NMIBC	All	95.1	(94.6-95.5)	92.2	(91.6-92.8)
	<50	97.6	(96.3-98.4)	96	(94.3-97.2)
	50-70	94.8	(94.4-95.3)	91.8	(91.1-92.4)
MIBC	All	45.9	(44.0-47.8)	43.1	(41.1-45.0)
	<50	42.22	(34.5-49.7)	39.4	(31.7-47.1)
	50-70	46.1	(44.2-48.1)	43.3	(41.3-45.3)

NMIBC – non-muscle invasive bladder cancer; MIBC – muscle invasive bladder cancer