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The UroLife study: A prospective cohort on dietary and lifestyle habits in relation to non-muscle-invasive bladder cancer prognosis and health-related quality of life

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Manuscripts

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3 1 **The UroLife study: A prospective cohort on dietary and lifestyle habits in relation to**
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5 2 **non-muscle-invasive bladder cancer prognosis and health-related quality of life**
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2
3 **21 ABSTRACT**

4
5 **22 Introduction:**

6
7 **23** Patients with non-muscle-invasive bladder cancer (NMIBC) have a good survival but are at
8
9 **24** high risk for tumour recurrence and disease progression. It is important to identify lifestyle
10
11 **25** habits that may reduce the risk of recurrence and progression and improve health-related
12
13 **26** quality of life (HRQOL). This paper describes the rationale and design of the UroLife study.
14
15 **27** The main aim of this study is to evaluate whether dietary and other lifestyle habits are related
16
17 **28** to prognosis and HRQOL in patients with NMIBC.

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19
20 **29 Methods and analysis:**

21
22 **30** The UroLife study is a multi-centre prospective cohort study among more than 1,100 newly
23
24 **31** diagnosed patients with NMIBC recruited from 22 hospitals in the Netherlands. At six weeks
25
26 **32** and three, 15, and 51 months after diagnosis, participants fill out a general questionnaire,
27
28 **33** and questionnaires about their dietary habits, lifestyle, and HRQOL. At three, 15, and 51
29
30 **34** months after diagnosis, information about fluid intake and micturition is collected with a
31
32 **35** four-day diary. At three and 15 months after diagnosis, patients donate blood samples
33
34 **36** for DNA extraction and (dietary) biomarker analysis. Tumour samples are collected
35
36 **37** from all patients with T1 disease to assess molecular subtypes. Information about
37
38 **38** disease characteristics and therapy for the primary tumour and subsequent recurrences is
39
40 **39** collected from the medical records by the Netherlands Cancer Registry.

41
42
43 **40 Ethics and dissemination:**

44
45 **41** The study protocol has been approved by the Committee for Human Research region
46
47 **42** Arnhem-Nijmegen (CMO 2013-494). Patients who agree to participate in the study provide
48
49 **43** written informed consent. The findings from our study will be disseminated through peer-
50
51 **44** reviewed scientific journals and presentations at (inter)national scientific meetings. Patients
52
53 **45** will be informed about the progress and results of this study through biannual newsletters
54
55 **46** and through the website of the study and of the bladder cancer patient association.

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57
58 **47**

1
2
3 48 **Keywords:** bladder cancer, diet, lifestyle, biomarkers, recurrence, prognosis, quality of life,
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5 49 cohort, study protocol
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11 51 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
12

- 13 52 • Large multicenter prospective cohort study of NMIBC patients recruited shortly after
14 diagnosis
15 53
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17 54 • Extensive dietary, lifestyle, medical, and HRQOL data at multiple time points after
18 diagnosis
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21 56 • Availability of blood samples at 3 and 15 months after diagnosis, and formalin-fixed,
22 paraffin-embedded tumour tissue
23 57
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25 58 • Limited power for subgroup analyses
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60 INTRODUCTION

61 Urinary bladder cancer (UBC) is the sixth most common cancer in the male population
62 worldwide and tenth if considering both genders.[1] Approximately 75% of patients is
63 diagnosed with non-muscle-invasive (NMIBC, stages Ta, T1, and Tis) and 25% with muscle-
64 invasive (MIBC, stages T2, T3, and T4) bladder cancer.[2] Patients with NMIBC have a good
65 survival but are at high risk for tumour recurrence and disease progression.[3] They are
66 therefore subjected to frequent follow-up by cystoscopy and treatment. This makes bladder
67 cancer the most expensive cancer in terms of health care expenditures per patient per
68 year.[4] The high recurrence rate may also impact health-related quality of life (HRQOL).[5]
69 Lifestyle factors have been linked to the prognosis and quality of life in patients with several
70 cancer types [6, 7] but evidence in patients with NMIBC is scarce. If we can identify dietary
71 and lifestyle habits that are related to the risk of recurrence and progression and HRQOL in
72 patients with NMIBC, optimal interventions can be developed to improve their prognosis and
73 HRQOL.

74 The primary risk factor for bladder cancer is smoking, which accounts for 43% of bladder
75 cancer cases in men and 26% in women in Europe.[8] Other important risk factors for
76 bladder cancer are occupational exposures to carcinogens like aromatic amines and
77 polycyclic aromatic hydrocarbons (PAHs), family history, and specific low penetrance
78 germline genetic variants.[9] Recent meta-analyses suggest that excess body weight [10]
79 and physical inactivity [11] may also increase bladder cancer risk. The World Cancer
80 Research Fund/American Institute for Cancer Research (The WCRF/AICR) report found
81 probable evidence that arsenic in drinking water increases the risk of bladder, and limited
82 suggestive evidence that higher consumption of fruit and vegetables and of tea decreases
83 the risk of bladder cancer.[12] For other dietary and lifestyle factors, this report concluded
84 that data were of too low quality, inconsistent, or the number of studies were insufficient to
85 draw conclusions.[12]

86 Available evidence about the role of lifestyle habits on prognosis in patients with NMIBC is
87 restricted to smoking [13, 14] and excess body weight.[15] A systematic review [13] and

1
2
3 88 recent meta-analysis of 10 studies including a total of 6,307 patients with NMIBC [14] found
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5 89 that current and former smokers at diagnosis had an approximately 25% increased risk of
6
7 90 recurrence compared to never smokers. Our recent meta-analysis [15] of three studies [16-
8
9 91 18] showed that overweight and obesity compared to normal weight at diagnosis were
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11 92 associated with increased risk of recurrence but not progression in patients with NMIBC,
12
13 93 although power for progression was limited.[15] Smoking cessation and weight loss after
14
15 94 diagnosis in relation to clinical outcomes has hardly been investigated. Evidence for other
16
17 95 lifestyle habits, such as fluid intake and micturition, physical activity, and fruit and vegetable
18
19 96 consumption, is very limited or not available.[15] Also, most studies on lifestyle and NMIBC
20
21 97 prognosis included a heterogeneous study population with different tumour stages and
22
23 98 grades of bladder cancer. However, NMIBC prognosis is clearly different for these subgroups
24
25 99 [19] and may also differ by molecular subtype.[20, 21] Whether associations of lifestyle
26
27 100 habits with NMIBC prognosis are mediated and/or modified by tumour stage and by
28
29 101 molecular subtype has not yet been investigated.

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31
32 102 Despite the high frequency of surveillance and repeated treatments, relatively little is known
33
34 103 about the HRQOL of patients with NMIBC,[22] and research with validated bladder cancer-
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36 104 specific instruments is needed.[23] A systematic review of five studies on lifestyle and
37
38 105 HRQOL in bladder cancer patients found some evidence for a positive association between
39
40 106 physical activity and HRQOL, but insufficient evidence to draw any conclusions for
41
42 107 consumption of fruit and vegetables or smoking cessation.[24]

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45 108 There is a clear need to obtain more insight in the relation between lifestyle habits (and habit
46
47 109 changes) and NMIBC outcomes and whether this relation is mediated and/or modified by
48
49 110 tumour stage and molecular subtype. This information is essential to develop personalized
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51 111 evidence-based lifestyle advice for patients with NMIBC to improve their prognosis and
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53 112 quality of life. This would enable patients to get some control over their own disease course.

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114 **METHODS AND ANALYSIS**

115 The UroLife study (**U**rothelial cell cancer: **L**ifestyle, prognosis, and quality of **L**ife) is a
116 prospective cohort study including patients with newly diagnosed NMIBC. The study has
117 been designed to evaluate the association of dietary and lifestyle habits with risk of
118 recurrence and progression and HRQOL. Patients are recruited in 22 hospitals in the East,
119 South, and Central part of the Netherlands. Before the start of the study, permission was
120 asked from all urologists of the participating hospitals to select and invite eligible patients
121 from the Netherlands Cancer Registry (NCR), held by the Netherlands Comprehensive
122 Cancer Organisation (IKNL). Once every 1 to 2 weeks, new patients are identified through
123 IKNL using notification lists of the nationwide network and registry of histo- and
124 cytopathology in the Netherlands (PALGA foundation). Approximately 4 weeks after
125 diagnosis, patients are invited on behalf of their urologist to participate in this study. Patients
126 who agree to participate provide a written informed consent.

128 **Patient population**

129 Eligible participants are Dutch speaking patients between 18 and 80 years old who are newly
130 diagnosed with a histologically confirmed primary stage Ta, T1, and Tis NMIBC tumour and
131 underwent a transurethral resection. Patients with a previous diagnosis of cancer in the past
132 five years and those with a lymph node metastasis or distant metastasis are not eligible.

134 **Patient and public involvement**

135 Patients were not involved in the design, recruitment and conduct of the study.

137 **Data collection and management**

138 *Questionnaires*

139 Participants are asked to complete self-administered web-based or paper-and-pencil-based
140 questionnaires at six weeks (T6wk), three months (T3mo), 15 months (T15mo), and 51
141 months (T51mo) after diagnosis (Figure 1, Table 1). Web-based questionnaires are collected

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2
3 142 using the data collection tool of the Patient Reported Outcomes Following Initial treatment
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5 143 and Long term Evaluation of Survivorship (PROFILES) registry.[25] Follow-up telephone
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7 144 calls are made to non-responding participants and to respondents whose questionnaires
8
9 145 have missing items.

10
11 146 The baseline questionnaire contains questions on demographics (age, sex, ethnicity,
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13 147 education, living situation, occupation, marital status) and (family) history of cancer. All
14
15 148 questionnaires collect information about height, body weight, amount and frequency of
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17 149 alcohol consumption during week- and weekend days, smoking habits, comorbidities and
18
19 150 the use of medication. Information on smoking habits is collected in detail, including age or
20
21 151 date of starting and stopping smoking, number of cigarettes smoked per day, duration of
22
23 152 smoking, and passive exposure to smoking. Information about habitual physical activity is
24
25 153 collected by using the previously validated Short QUestionnaire to ASsess Health-
26
27 154 enhancing physical activity (SQUASH),[26] which is fairly reliable and valid in an adult
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29 155 population.[26-28] The SQUASH questionnaire assesses the average time, i.e. number of
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31 156 days per week and hours and minutes per day, spent in commuting activities, leisure
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33 157 time activities, household activities, and activities at work in a normal week in the past
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35 158 month. At T3mo, T15mo, and T51mo, patients are also asked to measure and report their
36
37 159 waist and hip circumference.
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43 161 Habitual dietary intake is collected using a 163-item validated and reproducible self-
44
45 162 administered food frequency questionnaire that was developed by Wageningen
46
47 163 University.[29] The questionnaire contains questions about the frequency of consumption of
48
49 164 food products and the portion size during the previous year (T6wk) or the previous months
50
51 165 (T3mo, T15mo, and T51mo). Frequency and portion size of consumed food products are
52
53 166 multiplied to obtain their intake in grams per day. Nutrient intake is calculated using the
54
55 167 Dutch Food Composition Database (NEVO 2011).[30] Information about fluid intake and
56
57 168 micturition is collected with a four-day diary at T3mo, T15mo en T51mo.
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3 170 HRQOL is assessed at all four time points with the validated EORTC QLQ-C30 [31] and a 24-
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5 171 item module for patients with NMIBC, i.e. the EORTC QLQ-NMIBC24.[32] The EORTC QLQ-
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7 172 C30 contains five function scales (physical, role, cognitive, emotional and social functioning),
8
9 173 three symptom scales (fatigue, nausea, pain and vomiting) and six single items (dyspnea,
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11 174 insomnia, loss of appetite, constipation, diarrhea, and financial impact), all scored from 1 (not
12
13 175 at all) to 4 (very much)) and a global health status scale with ranges from 1 (very poor) to 7
14
15 176 (excellent). The EORTC QLQ-NMIBC24 contains six scales (urinary symptoms, malaise, future
16
17 177 worries, bloating and flatulence, sexual function, and male sexual function) and five single
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19 178 items (intravesical treatment issues, sexual intimacy, risk of contaminating partner, sexual
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21 179 enjoyment, female sexual problems) scored from 1 (not at all) to 4 (very much). All scores will
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23 180 be linearly transformed to a 0 to 100 scale.
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28 182 Furthermore, at T3mo patients are asked to report whether they are aware of possible risk
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30 183 factors for (bladder) cancer, received lifestyle advice from their physician, and what their
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32 184 attitudes are towards physicians giving lifestyle advice.
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185 **Table 1** Overview of data collection in UroLife at the four time points

Included topics	T6wk	T3mo	T15mo	T51mo	
Questionnaires					
<i>Sociodemographic data</i>	Date of birth, gender, living situation, marital status, country of birth of participant, father, mother, race, highest level of education, working history, occupational exposure	X			
<i>Anthropometry</i>	Height at diagnosis, weight two years before diagnosis, weight at age 18 years, average weight during adult life	X			
	Current body weight, waist and hip circumference	X	X	X	X
<i>Lifestyle</i>	Current and past smoking behaviour, environmental smoke exposure	X	X	X	X
	Short Questionnaire to Assess Health-enhancing physical activity [26]	X	X	X	X
	Frequency and amount of alcohol consumption during week and weekend days	X	X	X	X
	Changes in eating habits and reasons for/type of changes		X	X	X
<i>Medical history</i>	Previously diagnosed with cancer, family history of cancer	X			
	Comorbidities, medication use, dietary supplement use	X	X	X	X
<i>Questions for females</i>	Menstruation, menopause, use of contraceptives, use of hormone replacement therapy	X	X	X	X
	Pregnancy	X			
<i>Diet</i>	163- item Food Frequency Questionnaire	X	X	X	X
<i>HRQOL</i>	EORTC QLQ-C30 [31] and EORTC QLQ-NMIBC24 [32]	X	X	X	X
<i>Awareness risk factors and lifestyle advice</i>	Awareness of cancer risk factors, received lifestyle advice, attitudes towards lifestyle advice		X		
Four-day diary					
	Frequency micturition, amount and type of fluid intake		X	X	X
Blood					
	EDTA whole blood for DNA isolation		X		
	EDTA plasma, heparin plasma		X	X	
Tissue					
	Formalin-fixed paraffin-embedded tissue of the primary tumour	X			
Clinical data					
	Disease characteristics, therapy	X	X	X	X
	Recurrence and progression			X	X

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3 187 *Blood samples*
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5 188 Non-fasting blood samples are collected at T3mo and T15mo. At T3mo, 10 ml EDTA
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7 189 whole blood (for DNA isolation), 10 ml EDTA plasma and 10 ml heparin plasma is
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9 190 collected. At T15mo, 10 ml EDTA plasma and 10 ml heparin plasma is collected.
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11 191 Heparin plasma tubes are wrapped in aluminum foil to protect them from light. All blood
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13 192 samples are collected, processed and stored at -80°C locally in the participating
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15 193 hospitals according to a standard protocol before transportation on dry ice to the
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17 194 Radboud Biobank. The blood samples are stored in the Radboud Biobank at -80°C for
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19 195 future analyses of genetic and other biomarkers. Analysis of heparin plasma levels of
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21 196 nine biomarkers of fruit and vegetable consumption is planned. Concentration of six
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23 197 carotenoids (i.e. alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, lycopene
24
25 198 and zeaxanthin), alpha-tocopherol, beta- and gamma-tocopherol and retinol were
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27 199 measured by HPLC (Thermo Scientific Accela LC system; Thermo Fisher Scientific) and
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29 200 analyzed by using ChromQuest 5.0, Version 3.2.1 software (Thermo Fisher Scientific).
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34 202 *Tumour samples*
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36 203 From patients diagnosed with T1 NMIBC, tumour specimens will be collected in two batches
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38 204 in 2019 and 2021. Tumour blocks will be identified by using the PALGA foundation and
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40 205 retrieved using the Dutch National Tissuebank Portal (DNTP) from the local pathology
41
42 206 laboratories. Pathology review will be performed and tissue microarrays will be constructed.
43
44 207 Molecular subtypes will be assessed by immunohistochemistry in 2021. As the development
45
46 208 of a molecular classification system for NMIBC is still in progress and no consensus system
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48 209 is available yet,[33] we will use the most suitable evidence-based subtyping method that will
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50 210 then be available.
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55 212 *Clinical data*
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57 213 For all patients with NMIBC, information about disease characteristics and therapy for the
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59 214 initial tumour and subsequent recurrences is collected from the medical records by data

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2
3 215 managers of the Netherlands Cancer Registry. Information about tumour characteristics
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5 216 includes incidence date, clinical (cTNM) and post-surgical (pTNM) stage,[34] tumour grade,
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7 217 concomitant carcinoma in situ, multifocality, number of tumours and histology. With respect
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9 218 to therapy, information is collected on type of cystoscopy (white or blue light) and on
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11 219 transurethral resection (TUR), i.e. date of TUR, presence of detrusor in the surgical
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13 220 specimen, and presence of lymphovascular invasion. Furthermore, data on local treatment
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15 221 (e.g., intravesical chemotherapy, BCG) with start and stop dates and, if applicable, on
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17 222 cystectomy (e.g., date, type) are collected.
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22 224 Data on clinical outcomes, i.e. recurrence and progression with dates of diagnosis, stage and
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24 225 grade, is also collected.
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27 28 227 **Power considerations & Data analysis**

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30 228 The association of lifestyle factors with risk of recurrence and progression will be evaluated
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32 229 by estimating hazard ratios and 95% confidence intervals using Cox proportional hazards
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34 230 regression analyses. All analyses will be adjusted for age, gender, tumour characteristics,
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36 231 and other potential confounders. Analytical techniques for longitudinal data and multiple
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38 232 outcomes will also be considered. Our power calculation is based on 1,100 patients who will
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40 233 be followed for five years. For comparing the highest (n=275) vs. lowest quartile (n=275) of a
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42 234 lifestyle factor (or vice versa), this study will be sufficiently powered (two-sided alpha=0.05,
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44 235 power 80%) to detect a hazard ratio of ≥ 1.5 or ≥ 1.3 (or ≤ 0.7 or ≤ 0.8) when assuming a five-
45
46 236 year recurrence risk of 31% or 78%, [35] respectively. [36, 37] With an assumed loss to follow-
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48 237 up of 25% after five years, detectable hazard ratios will increase to ≥ 1.6 or ≥ 1.4 (or ≤ 0.6 or
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50 238 ≤ 0.7), respectively. Lower hazard ratios can be detected when lifestyle factors are modeled
51
52 239 continuously.
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54
55 240 The association of lifestyle factors with HRQOL will be evaluated using longitudinal mixed
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57 241 model analyses, taking into account the within-subject variation in lifestyle and HRQOL over
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59 242 time and the between-subject variation. All analyses will be adjusted for age, gender, tumour

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3 243 characteristics, and other potential confounders. Since we expect that the between-subject
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5 244 variation in lifestyle and HRQOL will be much larger than the within-subject variation, most
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7 245 information will come from the association observed between subjects and not from the
8
9 246 association observed within subjects over time, Therefore, our power calculation is based on
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11 247 a cross-sectional correlation at one time point. With 825 patients (assuming a drop-out of
12
13 248 25%) and using 10 predictor variables, we have 80% power to detect a small correlation
14
15 249 (Cohen's f^2 of 0.02).[38, 39] Power will be higher when using repeated measurements over
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17 250 time, especially when there is within-subject variation of lifestyle factors and HRQOL over
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19 251 time.
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23 24 253 **Cohort status**

25
26 254 Medical ethical approval was obtained on 17 January 2014. Patient recruitment started in
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28 255 May 2014. Between 8 May 2014 and 25 April 2017, 2,133 patients with NMIBC initially
29
30 256 diagnosed with Ta, T1, or Tis tumours have been identified and invited to participate in
31
32 257 UroLife. Of these invited patients, 1,193 patients agreed to participate and 77 dropped out
33
34 258 before filling out the first questionnaires (response rate 52%). Since May 2017, recruitment of
35
36 259 patients with T1 (but not Ta or Tis) tumours has continued and is still ongoing. We aim to
37
38 260 recruit a total of at least 700 patients with T1 bladder cancer, and the projected date of
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40 261 recruitment completion is April 2021.
41
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44 45 263 **DISCUSSION**

46
47 264 The UroLife study is one of the largest multicenter prospective cohort studies on lifestyle and
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49 265 NMIBC outcomes worldwide. UroLife will provide new and comprehensive insights into
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51 266 whether lifestyle habits (or habit changes) are related to NMIBC outcomes and HRQOL, and
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53 267 whether these relations differ by tumour stage and molecular subtype. Unique features of
54
55 268 UroLife are the recruitment of patients shortly after diagnosis, collection of extensive dietary,
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57 269 lifestyle, medical, and HRQOL data at multiple time points after diagnosis, collection of blood
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3 270 (for DNA and biomarker analysis), and the availability of tumour tissue samples (for
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5 271 molecular classification).
6

7 272 As in many prospective cohort studies, non-participation and loss to follow may limit the
8
9 273 generalizability of our findings. Although our study is large, we intend to combine our dataset
10
11 274 in the future with other similar prospective studies in NMIBC to increase statistical power for
12
13 275 subgroup analyses. Our ultimate aim is to provide personalized evidence-based lifestyle
14
15 276 advice to patients with NMIBC, also according to tumour stage and molecular subtype, to
16
17 277 enable them to have an influence on their clinical outcome.
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20 278

21 22 279 **ETHICS AND DISSEMINATION**

23
24 280 The study protocol has been approved by the Committee for Human Research region
25
26 281 Arnhem-Nijmegen (CMO 2013-494). Patients who agree to participate in the study provide
27
28 282 written informed consent. The findings from our cohort study will be disseminated through
29
30 283 peer-reviewed scientific journals, and presentations at (inter)national scientific meetings.
31
32 284 Patients will be informed about the progress and results of this study through biannual
33
34 285 newsletters and through the website of the study (<https://www.radboudumc.nl/trials/urolife>)
35
36 286 and of the bladder cancer patient association (<https://www.blaasofnierkanker.nl/>). Also,
37
38 287 presentations will be given at contact days of the bladder cancer patient association.
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3 288 **DECLARATIONS**
4

5 289

6
7 290 **Authors' contributions**
8

9 291 AV, LALMK, AJW, EK, and KKHA contributed to the conception and design of the study. AV
10
11 292 provides overall study management and coordinates the project. EW has contributed and
12
13 293 LdG contributes to data collection. LdG, EW and AV drafted the manuscript. All authors have
14
15 294 critically read and revised the manuscript. All authors approved the final version of the
16
17 295 manuscript.
18

19
20 296

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29
30 301 that will result from this study.
31

32 302

33
34 303 **Competing interests**
35

36 304 The authors declare that they have no competing interests.
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38 305

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40
41 306 **Availability of data and material**
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43 307 Data and material are not yet available since enrollment to the study is still ongoing and data
44
45 308 collection has not been completed yet. After completion of data collection, data will be made
46
47 309 available by the corresponding author upon reasonable request.
48

49 310

50
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52

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58
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4
5 317 P.L.M. van den Tillaar); Elkerliek Ziekenhuis, Helmond (Drs. E.W. Stapper †, Drs. P.J. van
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7 318 Hest); Gelre Ziekenhuizen, Apeldoorn/Zutphen (Drs. D.M. Bochove-Overgaauw); Isala
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18
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479 **FIGURE LEGENDS**

480 **Figure 1** Timeline and study design of the UroLife study.

For peer review only

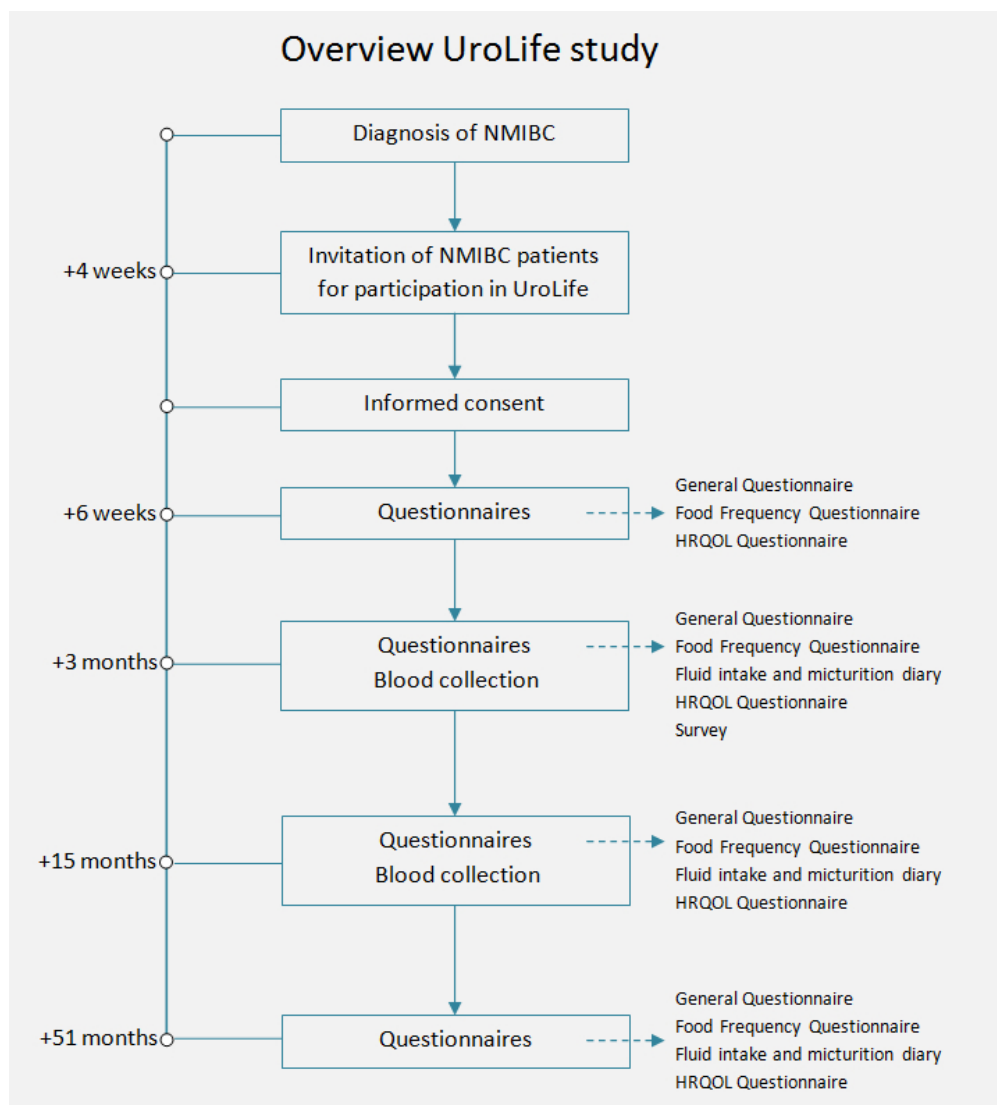


Figure 1 Timeline and study design of the UroLife study.

BMJ Open

The UroLife study: Protocol for a Dutch prospective cohort on lifestyle habits in relation to non-muscle-invasive bladder cancer prognosis and health-related quality of life

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Manuscripts

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5 2 **relation to non-muscle-invasive bladder cancer prognosis and health-related quality of**
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7 3 **life**
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22 **ABSTRACT**

23 **Introduction:**

24 Patients with non-muscle-invasive bladder cancer (NMIBC) have a good survival but are at
25 high risk for tumour recurrence and disease progression. It is important to identify lifestyle
26 habits that may reduce the risk of recurrence and progression and improve health-related
27 quality of life (HRQOL). This paper describes the rationale and design of the UroLife study.
28 The main aim of this study is to evaluate whether lifestyle habits are related to prognosis and
29 HRQOL in patients with NMIBC.

30 **Methods and analysis:**

31 The UroLife study is a multi-centre prospective cohort study among more than 1,100 newly
32 diagnosed patients with NMIBC recruited from 22 hospitals in the Netherlands. At six weeks
33 and three, 15, and 51 months after diagnosis, participants fill out a general questionnaire,
34 and questionnaires about their lifestyle habits and HRQOL. At three, 15, and 51 months after
35 diagnosis, information about fluid intake and micturition is collected with a four-day
36 diary. At three and 15 months after diagnosis, patients donate blood samples for DNA
37 extraction and (dietary) biomarker analysis. Tumour samples are collected from all
38 patients with T1 disease to assess molecular subtypes. Information about disease
39 characteristics and therapy for the primary tumour and subsequent recurrences is collected
40 from the medical records by the Netherlands Cancer Registry. Statistical analyses will be
41 adjusted for age, gender, tumour characteristics and other known confounders.

42 **Ethics and dissemination:**

43 The study protocol has been approved by the Committee for Human Research region
44 Arnhem-Nijmegen (CMO 2013-494). Patients who agree to participate in the study provide
45 written informed consent. The findings from our study will be disseminated through peer-
46 reviewed scientific journals and presentations at (inter)national scientific meetings. Patients
47 will be informed about the progress and results of this study through biannual newsletters
48 and through the website of the study and of the bladder cancer patient association.

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3 50 **Keywords:** bladder cancer, diet, lifestyle, biomarkers, recurrence, prognosis, quality of life,
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5 51 cohort, study protocol
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11 53 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 13 54 • Large multicenter prospective cohort study of NMIBC patients recruited shortly after
14 diagnosis
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17 56 • Extensive dietary, lifestyle, medical, and HRQOL data at multiple time points after
18 diagnosis
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21 58 • Availability of blood samples at 3 and 15 months after diagnosis, and formalin-fixed,
22 paraffin-embedded tumour tissue
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26 60 • Limited power for subgroup analyses
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28 61 • Loss to follow-up potentially influencing validity of results
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63 INTRODUCTION

64 Urinary bladder cancer is the sixth most common cancer in the male population worldwide
65 and tenth if considering both genders.[1] Approximately 75% of patients is diagnosed with
66 non-muscle-invasive (NMIBC, stages Ta, T1, and Tis) and 25% with muscle-invasive (MIBC,
67 stages T2, T3, and T4) bladder cancer.[2] Patients with NMIBC have a good survival but are
68 at high risk for tumour recurrence and disease progression.[3] They are therefore subjected
69 to frequent follow-up by cystoscopy and treatment. This makes bladder cancer the most
70 expensive cancer in terms of health care expenditures per patient per year.[4] The high
71 recurrence rate may also impact health-related quality of life (HRQOL).[5] Lifestyle factors
72 have been linked to the prognosis and quality of life in patients with several cancer types [6,
73 7] but evidence in patients with NMIBC is scarce. If we can identify lifestyle habits that are
74 related to the risk of recurrence and progression and HRQOL in patients with NMIBC,
75 optimal interventions can be developed to improve their prognosis and HRQOL.

76 The primary risk factor for bladder cancer is smoking, which accounts for 43% of bladder
77 cancer cases in men and 26% in women in Europe.[8] Other important risk factors for
78 bladder cancer are occupational exposures to carcinogens like aromatic amines and
79 polycyclic aromatic hydrocarbons (PAHs), family history, and specific low penetrance
80 germline genetic variants.[9] Recent meta-analyses suggest that excess body weight [10]
81 and physical inactivity [11] may also increase bladder cancer risk. The World Cancer
82 Research Fund/American Institute for Cancer Research (The WCRF/AICR) report found
83 probable evidence that arsenic in drinking water increases the risk of bladder, and limited
84 suggestive evidence that higher consumption of fruit and vegetables and of tea decreases
85 the risk of bladder cancer.[12] For other dietary and lifestyle factors, this report concluded
86 that data were of too low quality, inconsistent, or the number of studies were insufficient to
87 draw conclusions.[12]

88 Available evidence about the role of lifestyle habits on prognosis in patients with NMIBC is
89 restricted to smoking [13, 14] and excess body weight.[15] A systematic review [13] and
90 recent meta-analysis of 10 studies including a total of 6,307 patients with NMIBC [14] found

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3 91 that current and former smokers at diagnosis had an approximately 25% increased risk of
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5 92 recurrence compared to never smokers. Our recent meta-analysis [15] of three studies [16-
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7 93 18] showed that overweight and obesity compared to normal weight at diagnosis were
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9 94 associated with increased risk of recurrence but not progression in patients with NMIBC,
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11 95 although power for progression was limited.[15] Smoking cessation and weight loss after
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13 96 diagnosis in relation to clinical outcomes has hardly been investigated. Evidence for other
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15 97 lifestyle habits, such as fluid intake and micturition, physical activity, and fruit and vegetable
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17 98 consumption, is very limited or not available.[15] Also, most studies on lifestyle and NMIBC
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19 99 prognosis included a heterogeneous study population with different tumour stages and
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21 100 grades of bladder cancer. However, NMIBC prognosis is clearly different for these subgroups
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23 101 [19] and may also differ by molecular subtype.[20, 21] Whether associations of lifestyle
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25 102 habits with NMIBC prognosis are mediated and/or modified by tumour stage and by
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27 103 molecular subtype has not yet been investigated.

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29 104 Despite the high frequency of surveillance and repeated treatments, relatively little is known
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31 105 about the HRQOL of patients with NMIBC,[22] and research with validated bladder cancer-
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33 106 specific instruments is needed.[23] A systematic review of five studies on lifestyle and
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35 107 HRQOL in bladder cancer patients found some evidence for a positive association between
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37 108 physical activity and HRQOL, but insufficient evidence to draw any conclusions for
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39 109 consumption of fruit and vegetables or smoking cessation.[24]

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41 110 The aim of our study is to evaluate the association of pre- and post-diagnosis lifestyle habits
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43 111 (and habit changes) with risk of recurrence and progression and HRQOL. Also, we want to
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45 112 explore whether this association is mediated and/or modified by tumour stage and molecular
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115 **METHODS AND ANALYSIS**

116 The UroLife study (**U**rothelial cell cancer: **L**ifestyle, prognosis, and quality of **L**ife) is a
117 prospective cohort study including patients with newly diagnosed NMIBC. The study has
118 been designed to evaluate the association of lifestyle habits with risk of recurrence and
119 progression and HRQOL. Patients are recruited in 22 hospitals in the East, South, and
120 Central part of the Netherlands. Before the start of the study, permission was asked from all
121 urologists of the participating hospitals to select and invite eligible patients from the
122 Netherlands Cancer Registry (NCR), held by the Netherlands Comprehensive Cancer
123 Organisation (IKNL). Once every 1 to 2 weeks, new patients are identified through IKNL
124 using notification lists of the nationwide network and registry of histo- and cytopathology in
125 the Netherlands (PALGA foundation). Approximately 4 weeks after diagnosis, patients are
126 invited on behalf of their urologist to participate in this study. Patients who agree to
127 participate provide a written informed consent.

129 **Patient population**

130 Eligible participants are Dutch speaking patients between 18 and 80 years old who are newly
131 diagnosed with a histologically confirmed primary stage Ta, T1, and Tis NMIBC tumour and
132 underwent a transurethral resection. Patients with a previous diagnosis of cancer in the past
133 five years and those with a lymph node metastasis or distant metastasis are not eligible.

135 **Patient and public involvement**

136 Patients were not involved in the design, recruitment and conduct of the study.

138 **Data collection and management**

139 *Questionnaires*

140 Participants are asked to complete self-administered web-based or paper-and-pencil-based
141 questionnaires at six weeks (T6wk), three months (T3mo), 15 months (T15mo), and 51
142 months (T51mo) after diagnosis (Figure 1, Table 1). Web-based questionnaires are collected

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3 143 using the data collection tool of the Patient Reported Outcomes Following Initial treatment
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5 144 and Long term Evaluation of Survivorship (PROFILES) registry.[25] Follow-up telephone
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7 145 calls are made to non-responding participants and to respondents whose questionnaires
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9 146 have missing items.

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11 147 The baseline questionnaire contains questions on demographics (age, sex, ethnicity,
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13 148 education, living situation, occupation, marital status) and (family) history of cancer. All
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15 149 questionnaires collect information about height, body weight, amount and frequency of
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17 150 alcohol consumption during week- and weekend days, smoking habits, comorbidities and
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19 151 the use of medication. Information on smoking habits is collected in detail, including age or
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21 152 date of starting and stopping smoking, number of cigarettes smoked per day, duration of
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23 153 smoking, and passive exposure to smoking. Information about habitual physical activity is
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25 154 collected by using the previously validated Short QUestionnaire to ASsess Health-
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27 155 enhancing physical activity (SQUASH),[26] which is fairly reliable and valid in an adult
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29 156 population.[26-28] The SQUASH questionnaire assesses the average time, i.e. number of
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31 157 days per week and hours and minutes per day, spent in commuting activities, leisure
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33 158 time activities, household activities, and activities at work in a normal week in the past
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35 159 month. At T3mo, T15mo, and T51mo, patients are also asked to measure and report their
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37 160 waist and hip circumference.

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41 162 Habitual dietary intake is collected using a 163-item validated and reproducible self-
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43 163 administered food frequency questionnaire that was developed by Wageningen
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45 164 University.[29] The questionnaire contains questions about the frequency of consumption of
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47 165 food products and the portion size during the previous year (T6wk) or the previous months
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49 166 (T3mo, T15mo, and T51mo). Frequency and portion size of consumed food products are
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51 167 multiplied to obtain their intake in grams per day. Nutrient intake is calculated using the
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53 168 Dutch Food Composition Database (NEVO 2011).[30] Information about fluid intake and
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55 169 micturition is collected with a four-day diary at T3mo, T15mo en T51mo.

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3 171 HRQOL is assessed at all four time points with the validated European Organisation for
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5 172 Research and Treatment of Cancer (EORTC) QLQ-C30 [31] and a 24-item module for patients
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7 173 with NMIBC, i.e. the EORTC QLQ-NMIBC24.[32] The EORTC QLQ-C30 contains five function
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9 174 scales (physical, role, cognitive, emotional and social functioning), three symptom scales
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11 175 (fatigue, nausea, pain and vomiting) and six single items (dyspnea, insomnia, loss of appetite,
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13 176 constipation, diarrhea, and financial impact), all scored from 1 (not at all) to 4 (very much)) and
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15 177 a global health status scale with ranges from 1 (very poor) to 7 (excellent). The EORTC QLQ-
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17 178 NMIBC24 contains six scales (urinary symptoms, malaise, future worries, bloating and
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19 179 flatulence, sexual function, and male sexual function) and five single items (intravesical
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21 180 treatment issues, sexual intimacy, risk of contaminating partner, sexual enjoyment, female
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23 181 sexual problems) scored from 1 (not at all) to 4 (very much). All scores will be linearly
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25 182 transformed to a 0 to 100 scale.
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30 184 Furthermore, at T3mo patients are asked to report whether they are aware of possible risk
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32 185 factors for (bladder) cancer, received lifestyle advice from their physician, and what their
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34 186 attitudes are towards physicians giving lifestyle advice.
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187 **Table 1** Overview of data collection in UroLife at the four time points

Included topics	T6wk	T3mo	T15mo	T51mo	
Questionnaires					
<i>Sociodemographic data</i>	Date of birth, gender, living situation, marital status, country of birth of participant, father, mother, race, highest level of education, working history, occupational exposure	X			
<i>Anthropometry</i>	Height at diagnosis, weight two years before diagnosis, weight at age 18 years, average weight during adult life	X			
	Current body weight, waist and hip circumference	X	X	X	X
<i>Lifestyle</i>	Current and past smoking behaviour, environmental smoke exposure	X	X	X	X
	Short Questionnaire to Assess Health-enhancing physical activity [26]	X	X	X	X
	Frequency and amount of alcohol consumption during week and weekend days	X	X	X	X
	Changes in eating habits and reasons for/type of changes		X	X	X
<i>Medical history</i>	Previously diagnosed with cancer, family history of cancer	X			
	Comorbidities, medication use, dietary supplement use	X	X	X	X
<i>Questions for females</i>	Menstruation, menopause, use of contraceptives, use of hormone replacement therapy	X	X	X	X
	Pregnancy	X			
<i>Diet</i>	163- item Food Frequency Questionnaire	X	X	X	X
<i>HRQOL</i>	EORTC QLQ-C30 [31] and EORTC QLQ-NMIBC24 [32]	X	X	X	X
<i>Awareness risk factors and lifestyle advice</i>	Awareness of cancer risk factors, received lifestyle advice, attitudes towards lifestyle advice		X		
Four-day diary					
	Frequency micturition, amount and type of fluid intake		X	X	X
Blood					
	EDTA whole blood for DNA isolation		X		
	EDTA plasma, heparin plasma		X	X	
Tissue					
	Formalin-fixed paraffin-embedded tissue of the primary tumour	X			
Clinical data					
	Disease characteristics, therapy	X	X	X	X
	Recurrence and progression			X	X

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2
3 189 *Blood samples*
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5 190 Non-fasting blood samples are collected at T3mo and T15mo. At T3mo, 10 ml EDTA
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7 191 whole blood (for DNA isolation), 10 ml EDTA plasma and 10 ml heparin plasma is
8
9 192 collected. At T15mo, 10 ml EDTA plasma and 10 ml heparin plasma is collected.
10
11 193 Heparin plasma tubes are wrapped in aluminum foil to protect them from light. All blood
12
13 194 samples are collected, processed and stored at -80°C locally in the participating
14
15 195 hospitals according to a standard protocol before transportation on dry ice to the
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17 196 Radboud Biobank. The blood samples are stored in the Radboud Biobank at -80°C for
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19 197 future analyses of genetic and other biomarkers. Analysis of heparin plasma levels of
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21 198 nine biomarkers of fruit and vegetable consumption is planned. Concentration of six
22
23 199 carotenoids (i.e. alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, lycopene
24
25 200 and zeaxanthin), alpha-tocopherol, beta- and gamma-tocopherol and retinol were
26
27 201 measured by HPLC (Thermo Scientific Accela LC system; Thermo Fisher Scientific) and
28
29 202 analyzed by using ChromQuest 5.0, Version 3.2.1 software (Thermo Fisher Scientific).
30
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34 204 *Tumour samples*
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36 205 From patients diagnosed with T1 NMIBC, tumour specimens will be collected in two batches
37
38 206 in 2019 and 2021. Tumour blocks will be identified by using the PALGA foundation and
39
40 207 retrieved using the Dutch National Tissuebank Portal (DNTP) from the local pathology
41
42 208 laboratories. Pathology review will be performed and tissue microarrays will be constructed.
43
44 209 Molecular subtypes will be assessed by immunohistochemistry in 2021. As the development
45
46 210 of a molecular classification system for NMIBC is still in progress and no consensus system
47
48 211 is available yet,[33] we will use the most suitable evidence-based subtyping method that will
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50 212 then be available.
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55 214 *Clinical data*
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57 215 For all patients with NMIBC, information about disease characteristics and therapy for the
58
59 216 initial tumour is collected from the medical records by data managers of the Netherlands
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3 217 Cancer Registry. Information about tumour characteristics includes incidence date, clinical
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5 218 (cTNM) and post-surgical (pTNM) stage,[34] tumour grade, concomitant carcinoma in situ,
6
7 219 multifocality, number of tumours and histology. With respect to therapy, information is
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9 220 collected on type of cystoscopy (white or blue light) and on transurethral resection (TUR), i.e.
10
11 221 date of TUR, presence of detrusor in the surgical specimen, and presence of lymphovascular
12
13 222 invasion. Furthermore, data on local treatment (e.g., intravesical chemotherapy, BCG) with
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15 223 start and stop dates and, if applicable, on cystectomy (e.g., date, type) are collected.
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20 225 Data on clinical outcomes, i.e. recurrence and progression, with dates of diagnosis, tumour
21
22 226 characteristics, and therapy is also collected from the medical records by data managers of
23
24 227 the Netherlands Cancer Registry. Information on vital status is collected by linkage with the
25
26 228 Personal Records Database. All patients will be followed for at least 5 years.
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28 229

30 230 **Power considerations & Data analysis**

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32 231 Risk of recurrence (or progression) will be evaluated as time to first recurrence (or
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34 232 progression). The association of pre- and post-diagnostic lifestyle factors, as well as changes
35
36 233 in lifestyle factors, with risk of recurrence and progression will be evaluated by estimating
37
38 234 hazard ratios and 95% confidence intervals using Cox proportional hazards regression
39
40 235 analyses. All analyses will be adjusted for age, gender, tumour characteristics, and other
41
42 236 known confounders. Analytical techniques for longitudinal data and multiple outcomes will
43
44 237 also be explored and applied. Our power calculation is based on 1,100 patients who will be
45
46 238 followed for five years. For comparing the highest (n=275) vs. lowest quartile (n=275) of a
47
48 239 lifestyle factor (or vice versa), this study will be sufficiently powered (two-sided alpha=0.05,
49
50 240 power 80%) to detect a hazard ratio of ≥ 1.5 or ≥ 1.3 (or ≤ 0.7 or ≤ 0.8) when assuming a five-
51
52 241 year recurrence risk of 31% or 78%, [35] respectively. [36, 37] With an assumed loss to follow-
53
54 242 up of 25% after five years, detectable hazard ratios will increase to ≥ 1.6 or ≥ 1.4 (or ≤ 0.6 or
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56 243 ≤ 0.7), respectively. Lower hazard ratios can be detected when lifestyle factors are modeled
57
58 244 continuously.
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3 245 The association of lifestyle factors with HRQOL will be evaluated using longitudinal mixed
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5 246 model analyses, taking into account the within-subject variation in lifestyle and HRQOL over
6
7 247 time and the between-subject variation. All analyses will be adjusted for age, gender, tumour
8
9 248 characteristics, and other known confounders. Since we expect that the between-subject
10
11 249 variation in lifestyle and HRQOL will be much larger than the within-subject variation, most
12
13 250 information will come from the association observed between subjects and not from the
14
15 251 association observed within subjects over time, Therefore, our power calculation is based on
16
17 252 a cross-sectional correlation at one time point. With 825 patients (assuming a loss to follow-
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19 253 up of 25%) and using 10 predictor variables, we have 80% power to detect a small
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21 254 correlation (Cohen's f^2 of 0.02).[38, 39] Power will be higher when using repeated
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23 255 measurements over time, especially when there is within-subject variation of lifestyle factors
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25 256 and HRQOL over time.
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258 **Cohort status**

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32 259 Medical ethical approval was obtained on 17 January 2014. Patient recruitment started in
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34 260 May 2014. Between 8 May 2014 and 25 April 2017, 2,133 patients with NMIBC initially
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36 261 diagnosed with Ta, T1, or Tis tumours have been identified and invited to participate in
37
38 262 UroLife. Of these invited patients, 1,193 patients agreed to participate and 77 dropped out
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40 263 before filling out the first questionnaires (response rate 52%). Since May 2017, recruitment of
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42 264 patients with T1 (but not Ta or Tis) tumours has continued and is still ongoing. We aim to
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44 265 recruit a total of at least 700 patients with T1 bladder cancer, and the projected date of
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46 266 recruitment completion is April 2021.
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268 **DISCUSSION**

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52 269 The UroLife study is one of the largest multicenter prospective cohort studies on lifestyle and
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54 270 NMIBC outcomes worldwide. UroLife will provide new and comprehensive insights into
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56 271 whether lifestyle habits (or habit changes) are related to NMIBC outcomes and HRQOL, and
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58 272 whether these relations differ by tumour stage and molecular subtype. Unique features of
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3 273 UroLife are the recruitment of patients shortly after diagnosis, collection of extensive dietary,
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5 274 lifestyle, medical, and HRQOL data at multiple time points after diagnosis, collection of blood
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7 275 (for DNA and biomarker analysis), and the availability of tumour tissue samples (for
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9 276 molecular classification).

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11 277 As in many prospective cohort studies, non-participation may limit the generalisability of our
12
13 278 findings. In addition, loss to follow-up may limit the validity of our findings. Information bias
14
15 279 due to reliance on recall and self-report, or due to missing data, may be another potential
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17 280 limitation. Although our study is large, we intend to combine our dataset in the future with
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19 281 other similar prospective studies in NMIBC to increase statistical power for subgroup
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21 282 analyses.

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24 283 If the results of this study show that lifestyle factors are associated with clinical outcomes in
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26 284 NMIBC patients and these results are confirmed by other prospective studies or randomised
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28 285 trials, lifestyle recommendations and lifestyle interventions can be developed. Patients
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30 286 diagnosed with NMIBC could then be advised by their physician about their lifestyle and/or
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32 287 referred to a lifestyle intervention (e.g. smoking cessation program, exercise program). Thus,
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34 288 our ultimate aim is to provide personalized evidence-based lifestyle advice to patients with
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36 289 NMIBC, also according to tumour stage and molecular subtype, to enable them to have an
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38 290 influence on their clinical outcome.

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42 43 292 **ETHICS AND DISSEMINATION**

44
45 293 The study protocol has been approved by the Committee for Human Research region
46
47 294 Arnhem-Nijmegen (CMO 2013-494). Patients who agree to participate in the study provide
48
49 295 written informed consent. The findings from our cohort study will be disseminated through
50
51 296 peer-reviewed scientific journals, and presentations at (inter)national scientific meetings.
52
53 297 Patients will be informed about the progress and results of this study through biannual
54
55 298 newsletters and through the website of the study (<https://www.radboudumc.nl/trials/urolife>)
56
57 299 and of the bladder cancer patient association (<https://www.blaasofnierkanker.nl/>). Also,
58
59 300 presentations will be given at contact days of the bladder cancer patient association.

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3 301 **DECLARATIONS**
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6
7 303 **Authors' contributions**
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9 304 AV, LALMK, AJW, EK, and KKHA contributed to the conception and design of the study. AV
10
11 305 provides overall study management and coordinates the project. EW has contributed and
12
13 306 LdG contributes to data collection. LdG, EW and AV drafted the manuscript. All authors have
14
15 307 critically read and revised the manuscript. All authors approved the final version of the
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17 308 manuscript.
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29
30 314 that will result from this study.
31

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33 315

34 316 **Competing interests**
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36 317 The authors declare that they have no competing interests.
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41 319 **Availability of data and material**
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43 320 Data and material are not yet available since enrollment to the study is still ongoing and data
44
45 321 collection has not been completed yet. After completion of data collection, data will be made
46
47 322 available by the corresponding author upon reasonable request.
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50 323

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491 **FIGURE LEGENDS**

492 **Figure 1** Timeline and study design of the UroLife study.

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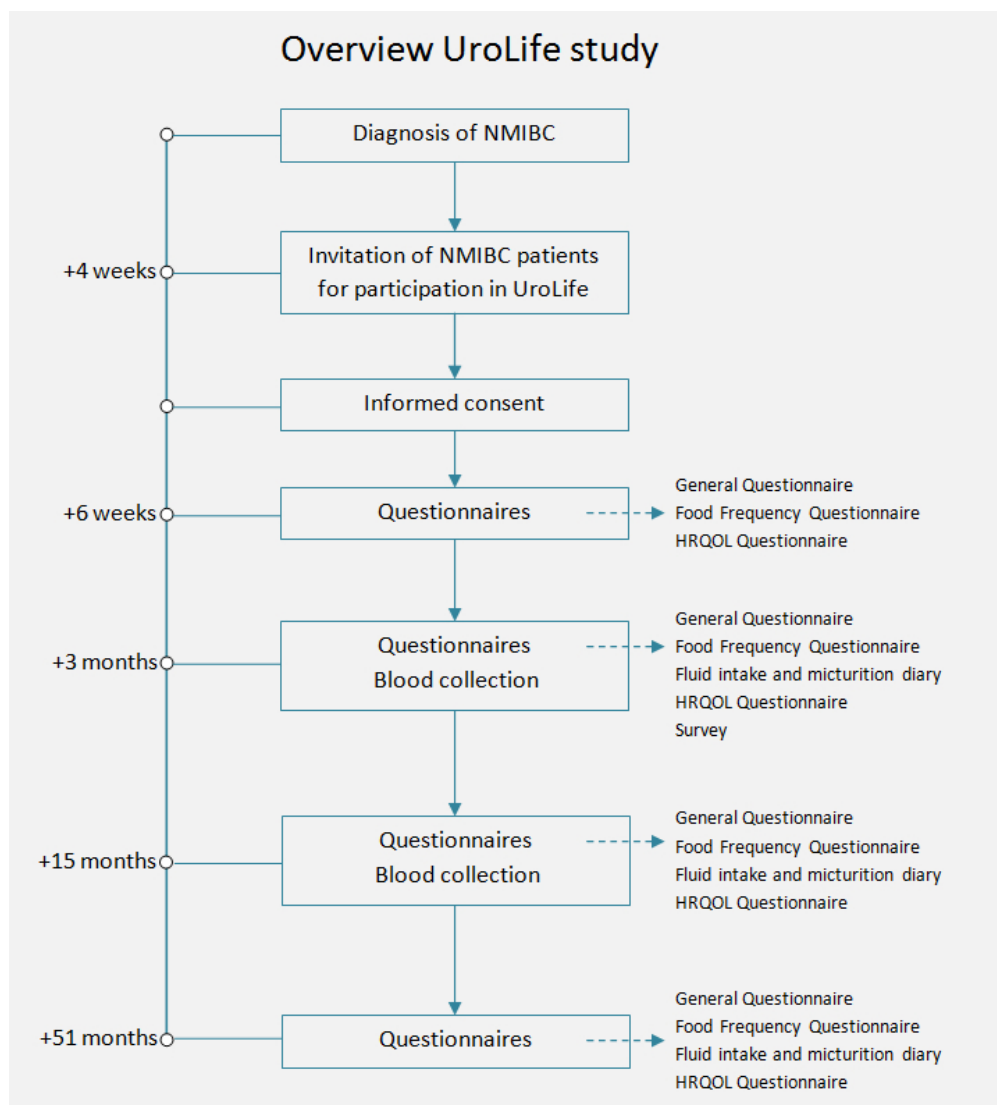


Figure 1 Timeline and study design of the UroLife study.

BMJ Open

The UroLife study: Protocol for a Dutch prospective cohort on lifestyle habits in relation to non-muscle-invasive bladder cancer prognosis and health-related quality of life

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Manuscripts

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3 1 **The UroLife study: Protocol for a Dutch prospective cohort on lifestyle habits in**
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22 **ABSTRACT**

23 **Introduction:**

24 Patients with non-muscle-invasive bladder cancer (NMIBC) have a good survival but are at
25 high risk for tumour recurrence and disease progression. It is important to identify lifestyle
26 habits that may reduce the risk of recurrence and progression and improve health-related
27 quality of life (HRQOL). This paper describes the rationale and design of the UroLife study.
28 The main aim of this study is to evaluate whether lifestyle habits are related to prognosis and
29 HRQOL in patients with NMIBC.

30 **Methods and analysis:**

31 The UroLife study is a multi-centre prospective cohort study among more than 1,100 newly
32 diagnosed patients with NMIBC recruited from 22 hospitals in the Netherlands. At six weeks
33 and three, 15, and 51 months after diagnosis, participants fill out a general questionnaire,
34 and questionnaires about their lifestyle habits and HRQOL. At three, 15, and 51 months after
35 diagnosis, information about fluid intake and micturition is collected with a four-day
36 diary. At three and 15 months after diagnosis, patients donate blood samples for DNA
37 extraction and (dietary) biomarker analysis. Tumour samples are collected from all
38 patients with T1 disease to assess molecular subtypes. Information about disease
39 characteristics and therapy for the primary tumour and subsequent recurrences is collected
40 from the medical records by the Netherlands Cancer Registry. Statistical analyses will be
41 adjusted for age, gender, tumour characteristics and other known confounders.

42 **Ethics and dissemination:**

43 The study protocol has been approved by the Committee for Human Research region
44 Arnhem-Nijmegen (CMO 2013-494). Patients who agree to participate in the study provide
45 written informed consent. The findings from our study will be disseminated through peer-
46 reviewed scientific journals and presentations at (inter)national scientific meetings. Patients
47 will be informed about the progress and results of this study through biannual newsletters
48 and through the website of the study and of the bladder cancer patient association.

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3 50 **Keywords:** bladder cancer, diet, lifestyle, biomarkers, recurrence, prognosis, quality of life,
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5 51 cohort, study protocol
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11 53 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 13 54 • Large multicenter prospective cohort study of NMIBC patients recruited shortly after
14 diagnosis
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17 56 • Extensive dietary, lifestyle, medical, and HRQOL data at multiple time points after
18 diagnosis
19 57
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21 58 • Availability of blood samples at 3 and 15 months after diagnosis, and formalin-fixed,
22 paraffin-embedded tumour tissue
23 59
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25 60 • Limited power for subgroup analyses
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28 61 • Loss to follow-up potentially influencing validity of results
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63 INTRODUCTION

64 Urinary bladder cancer is the sixth most common cancer in the male population worldwide
65 and tenth if considering both genders.[1] Approximately 75% of patients is diagnosed with
66 non-muscle-invasive (NMIBC, stages Ta, T1, and Tis) and 25% with muscle-invasive (MIBC,
67 stages T2, T3, and T4) bladder cancer.[2] Patients with NMIBC have a good survival but are
68 at high risk for tumour recurrence and disease progression.[3] They are therefore subjected
69 to frequent follow-up by cystoscopy and treatment. This makes bladder cancer the most
70 expensive cancer in terms of health care expenditures per patient per year.[4] The high
71 recurrence rate may also impact health-related quality of life (HRQOL).[5] Lifestyle factors
72 have been linked to the prognosis and quality of life in patients with several cancer types [6,
73 7] but evidence in patients with NMIBC is scarce. If we can identify lifestyle habits that are
74 related to the risk of recurrence and progression and HRQOL in patients with NMIBC,
75 optimal interventions can be developed to improve their prognosis and HRQOL.

76 The primary risk factor for bladder cancer is smoking, which accounts for 43% of bladder
77 cancer cases in men and 26% in women in Europe.[8] Other important risk factors for
78 bladder cancer are occupational exposures to carcinogens like aromatic amines and
79 polycyclic aromatic hydrocarbons (PAHs), family history, and specific low penetrance
80 germline genetic variants.[9] Recent meta-analyses suggest that excess body weight [10]
81 and physical inactivity [11] may also increase bladder cancer risk. The World Cancer
82 Research Fund/American Institute for Cancer Research (The WCRF/AICR) report found
83 probable evidence that arsenic in drinking water increases the risk of bladder, and limited
84 suggestive evidence that higher consumption of fruit and vegetables and of tea decreases
85 the risk of bladder cancer.[12] For other dietary and lifestyle factors, this report concluded
86 that data were of too low quality, inconsistent, or the number of studies were insufficient to
87 draw conclusions.[12]

88 Available evidence about the role of lifestyle habits on prognosis in patients with NMIBC is
89 restricted to smoking [13, 14] and excess body weight.[15] A systematic review [13] and
90 recent meta-analysis of 10 studies including a total of 6,307 patients with NMIBC [14] found

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3 91 that current and former smokers at diagnosis had an approximately 25% increased risk of
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5 92 recurrence compared to never smokers. Our recent meta-analysis [15] of three studies [16-
6
7 93 18] showed that overweight and obesity compared to normal weight at diagnosis were
8
9 94 associated with increased risk of recurrence but not progression in patients with NMIBC,
10
11 95 although power for progression was limited.[15] Smoking cessation and weight loss after
12
13 96 diagnosis in relation to clinical outcomes has hardly been investigated. Evidence for other
14
15 97 lifestyle habits, such as fluid intake and micturition, physical activity, and fruit and vegetable
16
17 98 consumption, is very limited or not available.[15] Also, most studies on lifestyle and NMIBC
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19 99 prognosis included a heterogeneous study population with different tumour stages and
20
21 100 grades of bladder cancer. However, NMIBC prognosis is clearly different for these subgroups
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23 101 [19] and may also differ by molecular subtype.[20, 21] Whether associations of lifestyle
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25 102 habits with NMIBC prognosis are mediated and/or modified by tumour stage and by
26
27 103 molecular subtype has not yet been investigated.

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29 104 Despite the high frequency of surveillance and repeated treatments, relatively little is known
30
31 105 about the HRQOL of patients with NMIBC,[22] and research with validated bladder cancer-
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33 106 specific instruments is needed.[23] A systematic review of five studies on lifestyle and
34
35 107 HRQOL in bladder cancer patients found some evidence for a positive association between
36
37 108 physical activity and HRQOL, but insufficient evidence to draw any conclusions for
38
39 109 consumption of fruit and vegetables or smoking cessation.[24]

40
41 110 The aim of our study is to evaluate the association of pre- and post-diagnosis lifestyle habits
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43 111 (and habit changes) with risk of recurrence and progression and HRQOL. Also, we want to
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45 112 explore whether this association is mediated and/or modified by tumour stage and molecular
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47 113 subtype.

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115 **METHODS AND ANALYSIS**

116 The UroLife study (**U**rothelial cell cancer: **L**ifestyle, prognosis, and quality of **L**ife) is a
117 prospective cohort study including patients with newly diagnosed NMIBC. The study has
118 been designed to evaluate the association of lifestyle habits with risk of recurrence and
119 progression and HRQOL. Patients are recruited in 22 hospitals in the East, South, and
120 Central part of the Netherlands. Before the start of the study, permission was asked from all
121 urologists of the participating hospitals to select and invite eligible patients from the
122 Netherlands Cancer Registry (NCR), held by the Netherlands Comprehensive Cancer
123 Organisation (IKNL). Once every 1 to 2 weeks, new patients are identified through IKNL
124 using notification lists of the nationwide network and registry of histo- and cytopathology in
125 the Netherlands (PALGA foundation). Approximately 4 weeks after diagnosis, patients are
126 invited on behalf of their urologist to participate in this study. Patients who agree to
127 participate provide a written informed consent.

129 **Patient population**

130 Eligible participants are Dutch speaking patients between 18 and 80 years old who are newly
131 diagnosed with a histologically confirmed primary stage Ta, T1, and Tis NMIBC tumour and
132 underwent a transurethral resection. Patients with a previous diagnosis of cancer in the past
133 five years and those with a lymph node metastasis or distant metastasis are not eligible.

135 **Patient and public involvement**

136 Patients were not involved in the design, recruitment and conduct of the study.

138 **Data collection and management**

139 *Questionnaires*

140 Participants are asked to complete self-administered web-based or paper-and-pencil-based
141 questionnaires at six weeks (T6wk), three months (T3mo), 15 months (T15mo), and 51
142 months (T51mo) after diagnosis (Figure 1, Table 1). Web-based questionnaires are collected

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3 143 using the data collection tool of the Patient Reported Outcomes Following Initial treatment
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5 144 and Long term Evaluation of Survivorship (PROFILES) registry.[25] Follow-up telephone
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7 145 calls are made to non-responding participants and to respondents whose questionnaires
8
9 146 have missing items.

10
11 147 The baseline questionnaire contains questions on demographics (age, sex, ethnicity,
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13 148 education, living situation, occupation, marital status) and (family) history of cancer. All
14
15 149 questionnaires collect information about height, body weight, amount and frequency of
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17 150 alcohol consumption during week- and weekend days, smoking habits, comorbidities and
18
19 151 the use of medication. Information on smoking habits is collected in detail, including age or
20
21 152 date of starting and stopping smoking, number of cigarettes smoked per day, duration of
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23 153 smoking, and passive exposure to smoking. Information about habitual physical activity is
24
25 154 collected by using the previously validated Short QUestionnaire to ASsess Health-
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27 155 enhancing physical activity (SQUASH),[26] which is fairly reliable and valid in an adult
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29 156 population.[26-28] The SQUASH questionnaire assesses the average time, i.e. number of
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31 157 days per week and hours and minutes per day, spent in commuting activities, leisure
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33 158 time activities, household activities, and activities at work in a normal week in the past
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35 159 month. At T3mo, T15mo, and T51mo, patients are also asked to measure and report their
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37 160 waist and hip circumference.

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39 161
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41 162 Habitual dietary intake is collected using a 163-item validated and reproducible self-
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43 163 administered food frequency questionnaire that was developed by Wageningen
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45 164 University.[29] The questionnaire contains questions about the frequency of consumption of
46
47 165 food products and the portion size during the previous year (T6wk) or the previous months
48
49 166 (T3mo, T15mo, and T51mo). Frequency and portion size of consumed food products are
50
51 167 multiplied to obtain their intake in grams per day. Nutrient intake is calculated using the
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53 168 Dutch Food Composition Database (NEVO 2011).[30] Information about fluid intake and
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55 169 micturition is collected with a four-day diary at T3mo, T15mo en T51mo.

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3 171 HRQOL is assessed at all four time points with the validated European Organisation for
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5 172 Research and Treatment of Cancer (EORTC) QLQ-C30 [31] and a 24-item module for patients
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7 173 with NMIBC, i.e. the EORTC QLQ-NMIBC24.[32] The EORTC QLQ-C30 contains five function
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9 174 scales (physical, role, cognitive, emotional and social functioning), three symptom scales
10
11 175 (fatigue, nausea, pain and vomiting) and six single items (dyspnea, insomnia, loss of appetite,
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13 176 constipation, diarrhea, and financial impact), all scored from 1 (not at all) to 4 (very much)) and
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15 177 a global health status scale with ranges from 1 (very poor) to 7 (excellent). The EORTC QLQ-
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17 178 NMIBC24 contains six scales (urinary symptoms, malaise, future worries, bloating and
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19 179 flatulence, sexual function, and male sexual function) and five single items (intravesical
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21 180 treatment issues, sexual intimacy, risk of contaminating partner, sexual enjoyment, female
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23 181 sexual problems) scored from 1 (not at all) to 4 (very much). All scores will be linearly
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25 182 transformed to a 0 to 100 scale.
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30 183
31 184 Furthermore, at T3mo patients are asked to report whether they are aware of possible risk
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33 185 factors for (bladder) cancer, received lifestyle advice from their physician, and what their
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35 186 attitudes are towards physicians giving lifestyle advice.
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187 **Table 1** Overview of data collection in UroLife at the four time points

Included topics	T6wk	T3mo	T15mo	T51mo	
Questionnaires					
<i>Sociodemographic data</i>	Date of birth, gender, living situation, marital status, country of birth of participant, father, mother, race, highest level of education, working history, occupational exposure	X			
<i>Anthropometry</i>	Height at diagnosis, weight two years before diagnosis, weight at age 18 years, average weight during adult life	X			
	Current body weight, waist and hip circumference	X	X	X	X
<i>Lifestyle</i>	Current and past smoking behaviour, environmental smoke exposure	X	X	X	X
	Short Questionnaire to Assess Health-enhancing physical activity [26]	X	X	X	X
	Frequency and amount of alcohol consumption during week and weekend days	X	X	X	X
	Changes in eating habits and reasons for/type of changes		X	X	X
<i>Medical history</i>	Previously diagnosed with cancer, family history of cancer	X			
	Comorbidities, medication use, dietary supplement use	X	X	X	X
<i>Questions for females</i>	Menstruation, menopause, use of contraceptives, use of hormone replacement therapy	X	X	X	X
	Pregnancy	X			
<i>Diet</i>	163- item Food Frequency Questionnaire	X	X	X	X
<i>HRQOL</i>	EORTC QLQ-C30 [31] and EORTC QLQ-NMIBC24 [32]	X	X	X	X
<i>Awareness risk factors and lifestyle advice</i>	Awareness of cancer risk factors, received lifestyle advice, attitudes towards lifestyle advice		X		
Four-day diary					
	Frequency micturition, amount and type of fluid intake		X	X	X
Blood					
	EDTA whole blood for DNA isolation		X		
	EDTA plasma, heparin plasma		X	X	
Tissue					
	Formalin-fixed paraffin-embedded tissue of the primary tumour	X			
Clinical data					
	Disease characteristics, therapy	X	X	X	X
	Recurrence and progression			X	X

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3 189 *Blood samples*
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5 190 Non-fasting blood samples are collected at T3mo and T15mo. At T3mo, 10 ml EDTA
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7 191 whole blood (for DNA isolation), 10 ml EDTA plasma and 10 ml heparin plasma is
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9 192 collected. At T15mo, 10 ml EDTA plasma and 10 ml heparin plasma is collected.
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11 193 Heparin plasma tubes are wrapped in aluminum foil to protect them from light. All blood
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13 194 samples are collected, processed and stored at -80°C locally in the participating
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15 195 hospitals according to a standard protocol before transportation on dry ice to the
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17 196 Radboud Biobank. The blood samples are stored in the Radboud Biobank at -80°C for
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19 197 future analyses of genetic and other biomarkers. Analysis of heparin plasma levels of
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21 198 nine biomarkers of fruit and vegetable consumption is planned. Concentration of six
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23 199 carotenoids (i.e. alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, lycopene
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25 200 and zeaxanthin), alpha-tocopherol, beta- and gamma-tocopherol and retinol were
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27 201 measured by HPLC (Thermo Scientific Accela LC system; Thermo Fisher Scientific) and
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29 202 analyzed by using ChromQuest 5.0, Version 3.2.1 software (Thermo Fisher Scientific).
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34 204 *Tumour samples*
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36 205 From patients diagnosed with T1 NMIBC, tumour specimens will be collected in two batches
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38 206 in 2019 and 2021. Tumour blocks will be identified by using the PALGA foundation and
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40 207 retrieved using the Dutch National Tissuebank Portal (DNTP) from the local pathology
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42 208 laboratories. Pathology review will be performed and tissue microarrays will be constructed.
43
44 209 Molecular subtypes will be assessed by immunohistochemistry in 2021. As the development
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46 210 of a molecular classification system for NMIBC is still in progress and no consensus system
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48 211 is available yet,[33] we will use the most suitable evidence-based subtyping method that will
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50 212 then be available.
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55 214 *Clinical data*
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57 215 For all patients with NMIBC, information about disease characteristics and therapy for the
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59 216 initial tumour is collected from the medical records by data managers of the Netherlands
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3 217 Cancer Registry. Information about tumour characteristics includes incidence date, clinical
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5 218 (cTNM) and post-surgical (pTNM) stage,[34] tumour grade, concomitant carcinoma in situ,
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7 219 multifocality, number of tumours and histology. With respect to therapy, information is
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9 220 collected on type of cystoscopy (white or blue light) and on transurethral resection (TUR), i.e.
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11 221 date of TUR, presence of detrusor in the surgical specimen, and presence of lymphovascular
12
13 222 invasion. Furthermore, data on local treatment (e.g., intravesical chemotherapy, BCG) with
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15 223 start and stop dates and, if applicable, on cystectomy (e.g., date, type) are collected.
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20 225 Data on clinical outcomes, i.e. recurrence and progression, with dates of diagnosis, tumour
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22 226 characteristics, and therapy is also collected from the medical records by data managers of
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24 227 the Netherlands Cancer Registry. Information on vital status is collected by linkage with the
25
26 228 Personal Records Database. All patients will be followed for at least 5 years.
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30 230 **Power considerations & Data analysis**

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32 231 Risk of recurrence (or progression) will be evaluated as time to first recurrence (or
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34 232 progression). The association of pre- and post-diagnostic lifestyle factors, as well as changes
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36 233 in lifestyle factors, with risk of recurrence and progression will be evaluated by estimating
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38 234 hazard ratios and 95% confidence intervals using Cox proportional hazards regression
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40 235 analyses. All analyses will be adjusted for age, gender, tumour characteristics, and other
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42 236 known confounders. Analytical techniques for longitudinal data and multiple outcomes will
43
44 237 also be explored and applied. Our power calculation is based on 1,100 patients who will be
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46 238 followed for five years. For comparing the highest (n=275) vs. lowest quartile (n=275) of a
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48 239 lifestyle factor (or vice versa), this study will be sufficiently powered (two-sided alpha=0.05,
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50 240 power 80%) to detect a hazard ratio of ≥ 1.5 or ≥ 1.3 (or ≤ 0.7 or ≤ 0.8) when assuming a five-
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52 241 year recurrence risk of 31% or 78%,[35] respectively.[36, 37] With an assumed loss to follow-
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54 242 up of 25% after five years, detectable hazard ratios will increase to ≥ 1.6 or ≥ 1.4 (or ≤ 0.6 or
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56 243 ≤ 0.7), respectively. Lower hazard ratios can be detected when lifestyle factors are modeled
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58 244 continuously.
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3 245 The association of lifestyle factors with HRQOL will be evaluated using longitudinal mixed
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5 246 model analyses, taking into account the within-subject variation in lifestyle and HRQOL over
6
7 247 time and the between-subject variation. All analyses will be adjusted for age, gender, tumour
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9 248 characteristics, and other known confounders. Since we expect that the between-subject
10
11 249 variation in lifestyle and HRQOL will be much larger than the within-subject variation, most
12
13 250 information will come from the association observed between subjects and not from the
14
15 251 association observed within subjects over time, Therefore, our power calculation is based on
16
17 252 a cross-sectional correlation at one time point. With 825 patients (assuming a loss to follow-
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19 253 up of 25%) and using 10 predictor variables, we have 80% power to detect a small
20
21 254 correlation (Cohen's f^2 of 0.02).[38, 39] Power will be higher when using repeated
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23 255 measurements over time, especially when there is within-subject variation of lifestyle factors
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25 256 and HRQOL over time.
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258 **Cohort status**

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32 259 Medical ethical approval was obtained on 17 January 2014. Patient recruitment started in
33
34 260 May 2014. Between 8 May 2014 and 25 April 2017, 2,133 patients with NMIBC initially
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36 261 diagnosed with Ta, T1, or Tis tumours have been identified and invited to participate in
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38 262 UroLife. Of these invited patients, 1,193 patients agreed to participate and 77 dropped out
39
40 263 before filling out the first questionnaires (response rate 52%). Since May 2017, recruitment of
41
42 264 patients with T1 (but not Ta or Tis) tumours has continued and is still ongoing. We aim to
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44 265 recruit a total of at least 700 patients with T1 bladder cancer, and the projected date of
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46 266 recruitment completion is April 2021.
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268 **DISCUSSION**

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52 269 The UroLife study is one of the largest multicenter prospective cohort studies on lifestyle and
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54 270 NMIBC outcomes worldwide. UroLife will provide new and comprehensive insights into
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56 271 whether lifestyle habits (or habit changes) are related to NMIBC outcomes and HRQOL, and
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58 272 whether these relations differ by tumour stage and molecular subtype. Unique features of
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3 273 UroLife are the recruitment of patients shortly after diagnosis, collection of extensive dietary,
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5 274 lifestyle, medical, and HRQOL data at multiple time points after diagnosis, collection of blood
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7 275 (for DNA and biomarker analysis), and the availability of tumour tissue samples (for
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9 276 molecular classification).

11 277 As in many prospective cohort studies, non-participation may limit the generalisability of our
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13 278 findings. In addition, loss to follow-up may limit the validity of our findings. Information bias
14
15 279 due to reliance on recall and self-report, or due to missing data, may be another potential
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17 280 limitation. Although our study is large, we intend to combine our dataset in the future with
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19 281 other similar prospective studies in NMIBC to increase statistical power for subgroup
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21 282 analyses.

24 283 If the results of this study show that lifestyle factors are associated with clinical outcomes in
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26 284 NMIBC patients and these results are confirmed by other prospective studies or randomised
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28 285 trials, lifestyle recommendations and lifestyle interventions can be developed. Patients
29
30 286 diagnosed with NMIBC could then be advised by their physician about their lifestyle and/or
31
32 287 referred to a lifestyle intervention (e.g. smoking cessation program, exercise program). Thus,
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34 288 our ultimate aim is to provide personalized evidence-based lifestyle advice to patients with
35
36 289 NMIBC, also according to tumour stage and molecular subtype, to enable them to have an
37
38 290 influence on their clinical outcome.

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42 43 292 **ETHICS AND DISSEMINATION**

45 293 The study protocol has been approved by the Committee for Human Research region
46
47 294 Arnhem-Nijmegen (CMO 2013-494). Patients who agree to participate in the study provide
48
49 295 written informed consent. The findings from our cohort study will be disseminated through
50
51 296 peer-reviewed scientific journals, and presentations at (inter)national scientific meetings.
52
53 297 Patients will be informed about the progress and results of this study through biannual
54
55 298 newsletters and through the website of the study (<https://www.radboudumc.nl/trials/urolife>)
56
57 299 and of the bladder cancer patient association (<https://www.blaasofnierkanker.nl/>). Also,
58
59 300 presentations will be given at contact days of the bladder cancer patient association.

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3 301 **DECLARATIONS**
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5 302

6
7 303 **Authors' contributions**
8

9 304 AV, LALMK, AJW, EK, and KKHA contributed to the conception and design of the study. AV
10
11 305 provides overall study management and coordinates the project. EW has contributed and
12
13 306 LdG contributes to data collection. LdG, EW and AV drafted the manuscript. All authors have
14
15 307 critically read and revised the manuscript. All authors approved the final version of the
16
17 308 manuscript.
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29
30 314 that will result from this study.
31

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34 316 **Competing interests**
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36 317 The authors declare that they have no competing interests.
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41 319 **Availability of data and material**
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43 320 Data and material are not yet available since enrollment to the study is still ongoing and data
44
45 321 collection has not been completed yet. After completion of data collection, data will be made
46
47 322 available by the corresponding author upon reasonable request.
48

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50 323

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52

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34
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491 **FIGURE LEGENDS**

492 **Figure 1** Timeline and study design of the UroLife study.

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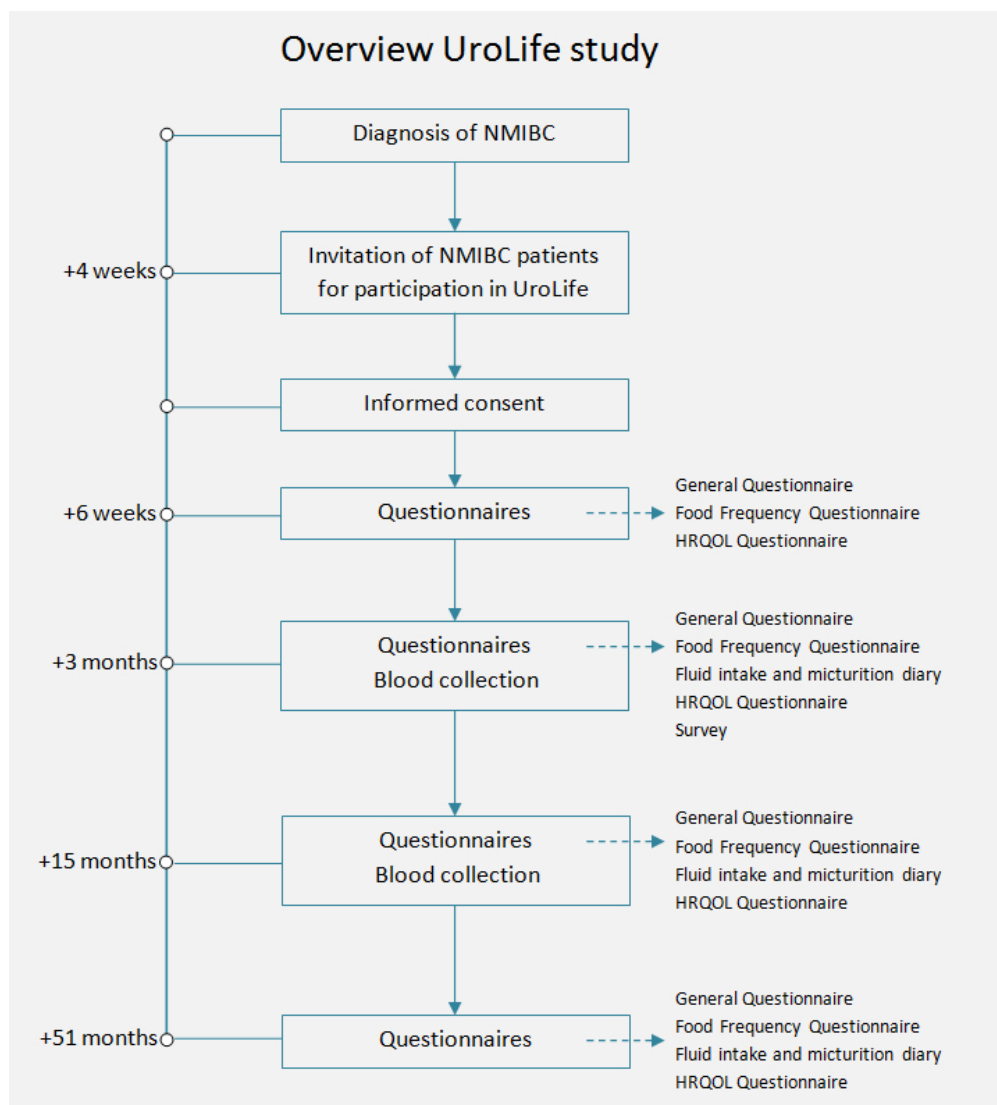


Figure 1 Timeline and study design of the UroLife study.