BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030396
Article Type:	Protocol
Date Submitted by the Author:	12-Mar-2019
Complete List of Authors:	de Goeij, Liesbeth; Radboudumc, Department for Health Evidence Westhoff, Ellen; Radboudumc, Department for Health Evidence Witjes, JA; Radboudumc, Department of Urology Aben, Katja; Netherlands Comprehensive Cancer Organisation; Radboudumc, Department for Health Evidence Kampman, Ellen; Wageningen University Kiemeney, B; Radboudumc, Department for Health Evidence Vrieling, Alina ; Radboudumc, Department for Health Evidence
Keywords:	Urological tumours < ONCOLOGY, EPIDEMIOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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

Liesbeth de Goeij[a], Ellen Westhoff[a], Alfred J. Witjes[b], Katja K.H. Aben[a,c], Ellen Kampman[d], Lambertus A.L.M. Kiemeney[a,b], Alina Vrieling[a*]

[a] Radboud university medical center, Radboud Institute for Health Sciences, Nijmegen, The Netherlands

[b] Radboud University Nijmegen Medical Center, Department of Urology, Nijmegen, The Netherlands

[c] Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands

[d] Wageningen University, Division of Human Nutrition and Health, Wageningen, The Netherlands

***Corresponding author:** Dr. Alina Vrieling, Radboud university medical center, Department for Health Evidence (Mailbox 133), P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel: +31 24 3616944, Fax: +31 24 3613505, e-mail: Alina.Vrieling@radboudumc.nl

Word count: 2973

ABSTRACT

Introduction:

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

Methods and analysis:

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

Ethics and dissemination:

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

Keywords: bladder cancer, diet, lifestyle, biomarkers, recurrence, prognosis, quality of life, cohort, study protocol

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Large multicenter prospective cohort study of NMIBC patients recruited shortly after diagnosis
- Extensive dietary, lifestyle, medical, and HRQOL data at multiple time points after diagnosis
- Availability of blood samples at 3 and 15 months after diagnosis, and formalin-fixed, paraffin-embedded tumour tissue
- Limited power for subgroup analyses

INTRODUCTION

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

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

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

recent meta-analysis of 10 studies including a total of 6,307 patients with NMIBC [14] found that current and former smokers at diagnosis had an approximately 25% increased risk of recurrence compared to never smokers. Our recent meta-analysis [15] of three studies [16-18] showed that overweight and obesity compared to normal weight at diagnosis were associated with increased risk of recurrence but not progression in patients with NMIBC, although power for progression was limited.[15] Smoking cessation and weight loss after diagnosis in relation to clinical outcomes has hardly been investigated. Evidence for other lifestyle habits, such as fluid intake and micturition, physical activity, and fruit and vegetable consumption, is very limited or not available.[15] Also, most studies on lifestyle and NMIBC prognosis included a heterogeneous study population with different tumour stages and grades of bladder cancer. However, NMIBC prognosis is clearly different for these subgroups [19] and may also differ by molecular subtype.[20, 21] Whether associations of lifestyle habits with NMIBC prognosis are mediated and/or modified by tumour stage and by molecular subtype has not yet been investigated.

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

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

METHODS AND ANALYSIS

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

Patient population

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

Patient and public involvement

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

Data collection and management

Questionnaires

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

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

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

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

HRQOL is assessed at all four time points with the validated EORTC QLQ-C30 [31] and a 24-item module for patients with NMIBC, i.e. the EORTC QLQ-NMIBC24.[32] The EORTC QLQ-C30 contains five function scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, nausea, pain and vomiting) and six single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial impact), all scored from 1 (not at all) to 4 (very much)) and a global health status scale with ranges from 1 (very poor) to 7 (excellent). The EORTC QLQ-NMIBC24 contains six scales (urinary symptoms, malaise, future worries, bloating and flatulence, sexual function, and male sexual function) and five single items (intravesical treatment issues, sexual intimacy, risk of contaminating partner, sexual enjoyment, female sexual problems) scored from 1 (not at all) to 4 (very much). All scores will be linearly transformed to a 0 to 100 scale.

Furthermore, at T3mo patients are asked to report whether they are aware of possible risk factors for (bladder) cancer, received lifestyle advice from their physician, and what their attitudes are towards physicians giving lifestyle advice.

Table 1 Overview of data collection in UroLife at the four time points

	Included topics	T6wk	T3mo	T15mo	T51mo
Questionnaires					
Sociodemographic data	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			
Anthropometry	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
Lifestyle	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
Medical history	Previously diagnosed with cancer, family history of cancer	X			
	Comorbidities, medication use, dietary supplement use	X	X	X	X
Questions for females	Menstruation, menopause, use of contraceptives, use of hormone replacement therapy	X	X	X	X
	Pregnancy	X			
Diet	163- item Food Frequency Questionnaire	X	X	X	X
HRQOL	EORTC QLQ-C30 [31] and EORTC QLQ-NMIBC24 [32]	X	X	X	X
Awareness risk factors and lifestyle advice	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

Blood samples

Non-fasting blood samples are collected at T3mo and T15mo. At T3mo, 10 ml EDTA whole blood (for DNA isolation), 10 ml EDTA plasma and 10 ml heparin plasma is collected. At T15mo, 10 ml EDTA plasma and 10 ml heparin plasma is collected. Heparin plasma tubes are wrapped in aluminum foil to protect them from light. All blood samples are collected, processed and stored at -80°C locally in the participating hospitals according to a standard protocol before transportation on dry ice to the Radboud Biobank. The blood samples are stored in the Radboud Biobank at -80°C for future analyses of genetic and other biomarkers. Analysis of heparin plasma levels of nine biomarkers of fruit and vegetable consumption is planned. Concentration of six carotenoids (i.e. alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, lycopene and zeaxanthin), alpha-tocopherol, beta- and gamma-tocopherol and retinol were measured by HPLC (Thermo Scientific Accela LC system; Thermo Fisher Scientific) and analyzed by using ChromQuest 5.0, Version 3.2.1 software (Thermo Fisher Scientific).

Tumour samples

From patients diagnosed with T1 NMIBC, tumour specimens will be collected in two batches in 2019 and 2021. Tumour blocks will be identified by using the PALGA foundation and retrieved using the Dutch National Tissuebank Portal (DNTP) from the local pathology laboratories. Pathology review will be performed and tissue microarrays will be constructed. Molecular subtypes will be assessed by immunohistochemistry in 2021. As the development of a molecular classification system for NMIBC is still in progress and no consensus system is available yet,[33] we will use the most suitable evidence-based subtyping method that will then be available.

Clinical data

For all patients with NMIBC, information about disease characteristics and therapy for the initial tumour and subsequent recurrences is collected from the medical records by data

managers of the Netherlands Cancer Registry. Information about tumour characteristics includes incidence date, clinical (cTNM) and post-surgical (pTNM) stage,[34] tumour grade, concomitant carcinoma in situ, multifocality, number of tumours and histology. With respect to therapy, information is collected on type of cystoscopy (white or blue light) and on transurethral resection (TUR), i.e. date of TUR, presence of detrusor in the surgical specimen, and presence of lymphovascular invasion. Furthermore, data on local treatment (e.g., intravesical chemotherapy, BCG) with start and stop dates and, if applicable, on cystectomy (e.g., date, type) are collected.

Data on clinical outcomes, i.e. recurrence and progression with dates of diagnosis, stage and grade, is also collected.

Power considerations & Data analysis

The association of lifestyle factors with risk of recurrence and progression will be evaluated by estimating hazard ratios and 95% confidence intervals using Cox proportional hazards regression analyses. All analyses will be adjusted for age, gender, tumour characteristics, and other potential confounders. Analytical techniques for longitudinal data and multiple outcomes will also be considered. Our power calculation is based on 1,100 patients who will be followed for five years. For comparing the highest (n=275) vs. lowest quartile (n=275) of a lifestyle factor (or vice versa), this study will be sufficiently powered (two-sided alpha=0.05, power 80%) to detect a hazard ratio of ≥1.5 or ≥1.3 (or ≤0.7 or ≤0.8) when assuming a five-year recurrence risk of 31% or 78%,[35] respectively.[36, 37] With an assumed loss to follow-up of 25% after five years, detectable hazard ratios will increase to ≥1.6 or ≥1.4 (or ≤0.6 or ≤0.7), respectively. Lower hazard ratios can be detected when lifestyle factors are modeled continuously.

The association of lifestyle factors with HRQOL will be evaluated using longitudinal mixed model analyses, taking into account the within-subject variation in lifestyle and HRQOL over time and the between-subject variation. All analyses will be adjusted for age, gender, tumour

characteristics, and other potential confounders. Since we expect that the between-subject variation in lifestyle and HRQOL will be much larger than the within-subject variation, most information will come from the association observed between subjects and not from the association observed within subjects over time, Therefore, our power calculation is based on a cross-sectional correlation at one time point. With 825 patients (assuming a drop-out of 25%) and using 10 predictor variables, we have 80% power to detect a small correlation (Cohen's f^2 of 0.02).[38, 39] Power will be higher when using repeated measurements over time, especially when there is within-subject variation of lifestyle factors and HRQOL over time.

Cohort status

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

DISCUSSION

The UroLife study is one of the largest multicenter prospective cohort studies on lifestyle and NMIBC outcomes worldwide. UroLife will provide new and comprehensive insights into whether lifestyle habits (or habit changes) are related to NMIBC outcomes and HRQOL, and whether these relations differ by tumour stage and molecular subtype. Unique features of UroLife are the recruitment of patients shortly after diagnosis, collection of extensive dietary, lifestyle, medical, and HRQOL data at multiple time points after diagnosis, collection of blood

(for DNA and biomarker analysis), and the availability of tumour tissue samples (for molecular classification).

As in many prospective cohort studies, non-participation and loss to follow may limit the generalizability of our findings. Although our study is large, we intend to combine our dataset in the future with other similar prospective studies in NMIBC to increase statistical power for subgroup analyses. Our ultimate aim is to provide personalized evidence-based lifestyle advice to patients with NMIBC, also according to tumour stage and molecular subtype, to enable them to have an influence on their clinical outcome.

ETHICS AND DISSEMINATION

The study protocol has been approved by the Committee for Human Research region Arnhem-Nijmegen (CMO 2013-494). Patients who agree to participate in the study provide written informed consent. The findings from our cohort study will be disseminated through peer-reviewed scientific journals, and presentations at (inter)national scientific meetings. Patients will be informed about the progress and results of this study through biannual newsletters and through the website of the study (https://www.radboudumc.nl/trials/urolife) and of the bladder cancer patient association (https://www.blaasofnierkanker.nl/). Also, presentations will be given at contact days of the bladder cancer patient association.

DECLARATIONS

Authors' contributions

AV, LALMK, AJW, EK, and KKHA contributed to the conception and design of the study. AV provides overall study management and coordinates the project. EW has contributed and LdG contributes to data collection. LdG, EW and AV drafted the manuscript. All authors have critically read and revised the manuscript. All authors approved the final version of the manuscript.

Funding

This work was supported by Alpe d'HuZes/Dutch Cancer Society (KUN 2013-5926) and Dutch Cancer Society (Project no. 11179). Sponsors were not involved in the study design nor will they be in the collection, analysis, and interpretation of data, or in the publications that will result from this study.

Competing interests

The authors declare that they have no competing interests.

Availability of data and material

Data and material are not yet available since enrollment to the study is still ongoing and data collection has not been completed yet. After completion of data collection, data will be made available by the corresponding author upon reasonable request.

Acknowledgements

We are grateful to all the patients who participate in this study and we would like to thank the following hospitals for their involvement in recruitment for the UroLife study: Amphia Ziekenhuis, Breda/Oosterhout (Drs. D.K.E. van der Schoot); Ziekenhuis Bernhoven, Uden (Drs. A.Q.H.J. Niemer); Canisius-Wilhelmina Ziekenhuis, Nijmegen (Dr. D.M. Somford);

Catharina Ziekenhuis, Eindhoven (Dr. E.L. Koldewijn); Deventer Ziekenhuis, Deventer (Drs. P.L.M. van den Tillaar); Elkerliek Ziekenhuis, Helmond (Drs. E.W. Stapper †, Drs. P.J. van Hest); Gelre Ziekenhuizen, Apeldoorn/Zutphen (Drs. D.M. Bochove-Overgaauw); Isala Klinieken, Zwolle (Dr. E. te Slaa); Jeroen Bosch Ziekenhuis, 's-Hertogenbosch (Dr. J.R. Oddens; Dr. S. van der Meer); Meander Medisch Centrum, Amersfoort (Drs. F.S. van Rey); Medisch Spectrum Twente, Enschede (Dr. M. Asselman); Maxima Medisch Centrum, Veldhoven/Eindhoven (Dr. L.M.C.L. Fossion); Maasziekenhuis Pantein, Boxmeer (Drs. E. van Boven); Radboudumc, Nijmegen (Prof. Dr. J.A. Witjes); Rijnstate, Arnhem/Velp/Zevenaar (Drs. C.J. Wijburg); Slingeland Ziekenhuis, Doetinchem (Drs. A.D.H. Geboers); St. Anna Ziekenhuis, Geldrop (Drs. A. Sonneveld); Elisabeth-TweeSteden Ziekenhuis, Tilburg/Waalwijk (Dr. P.J.M. Kil); St. Jansdal Ziekenhuis, Harderwijk (Drs. W.J. Kniestedt); VieCuri, Venlo (Drs. G. Yurdakul, Dr. A.H.P. Meier); Ziekenhuis Gelderse Vallei, Ede (Drs. M.D.H. Kortleve); Ziekenhuisgroep Twente, Almelo/Hengelo (Dr. E.B. Cornel). In addition, we thank Ms. Monique Eijgenberger for her assistance in data collection. We also thank the data managers and research assistants of the Netherlands Cancer Registry held by the Netherlands Comprehensive Cancer Organisation (IKNL) for inviting patients and collecting the clinical data.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394-424.

2. Babjuk M, Böhle A, Burger M, et al. EAU guidelines on non–muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol* 2017;71(3):447-61.

3. Cambier S, Sylvester RJ, Collette L, et al. EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guerin. *Eur Urol* 2016;69(1):60-9.

4. Sievert KD, Amend B, Nagele U, et al. Economic aspects of bladder cancer: what are the benefits and costs? *World J Urol* 2009;27(3):295-300.

5. Schmidt S, Francés A, Garin JAL, et al. Quality of life in patients with non–muscle-invasive bladder cancer: One-year results of a multicentre prospective cohort study. *Urol Oncol* 2015;33(1):19.e7-19.e15.

6. Ligibel J. Lifestyle factors in cancer survivorship. *J Clin Oncol* 2012;30(30):3697-704.

7. Mehra K, Berkowitz A, Sanft T. Diet, Physical Activity, and Body Weight in Cancer Survivorship. *Med Clin North Am*. 2017;101(6):1151-65.

8. van Osch FH, Jochems SH, van Schooten F-J, et al. Quantified relations between exposure to tobacco smoking and bladder cancer risk: a meta-analysis of 89 observational studies. *Int J Epidemiol* 2016;45(3):857-70.

9. Cumberbatch MGK, Jubber I, Black PC, et al. Epidemiology of Bladder Cancer: A Systematic Review and Contemporary Update of Risk Factors in 2018. *Eur Urol* 2018;74(6):784-95.

10. Sun J-W, Zhao L-G, Yang Y, et al. Obesity and risk of bladder cancer: a dose-response meta-analysis of 15 cohort studies. *PloS one* 2015;10(3):e0119313.

11. Keimling M, Behrens G, Schmid D, et al. The association between physical activity and bladder cancer: systematic review and meta-analysis. *Br J Cancer* 2014;110(7):1862-70.

12. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018: Diet, nutrition, physical activity and bladder cancer. 2018, https://www.wcrf.org/dietandcancer

13. Crivelli JJ, Xylinas E, Kluth LA, et al. Effect of smoking on outcomes of urothelial carcinoma: a systematic review of the literature. *Eur Urol* 2014;65(4):742-54.

14. Hou L, Hong X, Dai M, et al. Association of smoking status with prognosis in bladder cancer: A meta-analysis. *Oncotarget* 2017;8(1):1278-89.

15. Westhoff E, Witjes JA, Fleshner NE, et al. Body Mass Index, Diet-Related Factors, and Bladder Cancer Prognosis: A Systematic Review and Meta-Analysis. *Bladder Cancer* 2018;4(1):91-112.

16. Kluth LA, Xylinas E, Crivelli JJ, et al. Obesity is associated with worse outcomes in patients with T1 high grade urothelial carcinoma of the bladder. *J Urol* 2013;190(2):480-6.

17. Wyszynski A, Tanyos SA, Rees JR, et al. Body mass and smoking are modifiable risk factors for recurrent bladder cancer. *Cancer* 2014;120(3):408-14.

18. Xu T, Zhu Z, Wang X, et al. Impact of body mass on recurrence and progression in Chinese patients with Ta, T1 urothelial bladder cancer. *Int Urol Nephrol* 2015;47(7):1135-41.

19. van der Heijden AG, Witjes JA. Recurrence, progression, and follow-up in non–muscle-invasive bladder cancer. *Eur Urol Suppl* 2009;8(7):556-62.

20. Sjödahl G, Lauss M, Lövgren K, et al. A molecular taxonomy for urothelial carcinoma. *Clin Cancer Res* 2012;18:3377-86.

21. Patschan O, Sjödahl G, Chebil G, et al. A molecular pathologic framework for risk stratification of stage T1 urothelial carcinoma. *Eur Urol* 2015;68(5):824-32.

22. Jung A, Nielsen ME, Crandell JL, et al. Quality of Life in Non-Muscle-Invasive Bladder Cancer Survivors: A Systematic Review. *Cancer Nurs* Published Online First: 1 June 2018. doi:10.1097/NCC.0000000000000606.

23. Mohamed N, Gilbert F, Lee C, et al. Pursuing Quality in the application of bladder Cancer quality of Life Research. *Bladder Cancer* 2016;2(2):139-49.

24. Gopalakrishna A, Longo TA, Fantony JJ, et al. Lifestyle factors and health-related quality of life in bladder cancer survivors: a systematic review. *J Cancer Surviv* 2016;10(5):874-82.

25. van de Poll-Franse LV, Horevoorts N, van Eenbergen M, et al. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. *Eur J Cancer* 2011;47(14):2188-94.

26. Wendel-Vos GW, Schuit AJ, Saris WH, et al. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol* 2003;56(12):1163-9.

27. de Hollander EL, Zwart L, de Vries SI, et al. The SQUASH was a more valid tool than the OBiN for categorizing adults according to the Dutch physical activity and the combined guideline. *J Clin Epidemiol* 2012;65(1):73-81.

28. Wagenmakers R, van den Akker-Scheek I, Groothoff JW, et al. Reliability and validity of the short questionnaire to assess health-enhancing physical activity (SQUASH) in patients after total hip arthroplasty. *BMC Musculoskelet Disord* 2008;9(1):141.

29. Siebelink E, Geelen A, de Vries JH. Self-reported energy intake by FFQ compared with actual energy intake to maintain body weight in 516 adults. *Br J Nutr* 2011;106(2):274-81.

30. NEVO-tabel (2011) Dutch Food Composition Database. Den Haag: RIVM/Voedingscentrum.

31. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85(5):365-76.

32. Blazeby JM, Hall E, Aaronson NK, et al. Validation and reliability testing of the EORTC QLQ-NMIBC24 questionnaire module to assess patient-reported outcomes in non-muscle-invasive bladder cancer. *Eur Urol* 2014;66(6):1148-56.

33. Chandrasekar T, Erlich A, Zlotta AR. Molecular Characterization of Bladder Cancer. *Curr Urol Rep* 2018;19(12):107.

34. Babjuk M, Böhle A, Burger M, et al. EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder: Update 2016. *Eur Urol* 2017;71(3):447-61.

35. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006;49(3):466-77.

36. Dupont WD, Plummer WD. Power and sample size calculations: a review and computer program. *Control Clin Trials* 1990;11(2):116-28.

37. Dupont WD, Plummer WD. PS: Power and Sample Size Calculation. http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize. Accessed 16 January 2019.

38. Faul F, Erdfelder E, Buchner A, et al. Statistical power analyses using G* Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods* 2009;41(4):1149-60.

39. Faul F, Erdfelder E, Buchner A, et al. G*Power: Statistical Power Analyses for Windows and Mac. http://www.gpower.hhu.de. Accessed 16 January 2019.

FIGURE LEGENDS

Figure 1 Timeline and study design of the UroLife study.

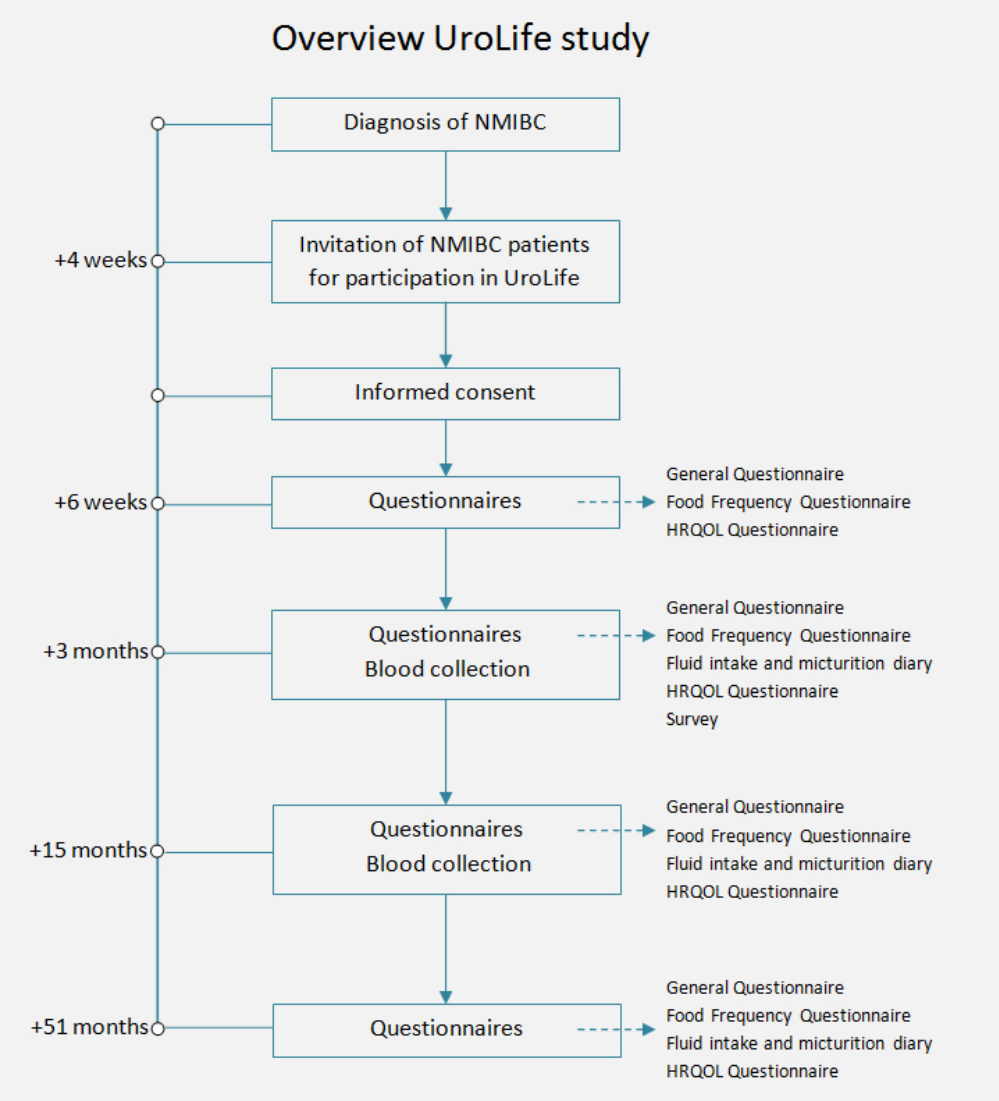

Figure 1 Timeline and study design of the UroLife study.

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030396.R1
Article Type:	Protocol
Date Submitted by the Author:	27-Aug-2019
Complete List of Authors:	de Goeij, Liesbeth; Radboudumc, Department for Health Evidence Westhoff, Ellen; Radboudumc, Department for Health Evidence Witjes, JA; Radboudumc, Department of Urology Aben, Katja; Netherlands Comprehensive Cancer Organisation; Radboudumc, Department for Health Evidence Kampman, Ellen; Wageningen University Kiemeney, Lambertus; Radboudumc, Department for Health Evidence Vrieling, Alina; Radboudumc, Department for Health Evidence
Primary Subject Heading:	Urology
Secondary Subject Heading:	Epidemiology
Keywords:	Urological tumours < ONCOLOGY, EPIDEMIOLOGY, NUTRITION & DIETETICS

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

Liesbeth de Goeij[a], Ellen Westhoff[a], J. Alfred Witjes[b], Katja K.H. Aben[a,c], Ellen Kampman[d], Lambertus A.L.M. Kiemeney[a,b], Alina Vrieling[a*]

[a] Radboud university medical center, Radboud Institute for Health Sciences, Nijmegen, The Netherlands

[b] Radboud University Nijmegen Medical Center, Department of Urology, Nijmegen, The Netherlands

[c] Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands

[d] Wageningen University, Division of Human Nutrition and Health, Wageningen, The Netherlands

***Corresponding author:** Dr. Alina Vrieling, Radboud university medical center, Department for Health Evidence (Mailbox 133), P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel: +31 24 3616944, Fax: +31 24 3613505, e-mail: Alina.Vrieling@radboudumc.nl

Word count: 3040

ABSTRACT

Introduction:

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

Methods and analysis:

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

Ethics and dissemination:

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

Keywords: bladder cancer, diet, lifestyle, biomarkers, recurrence, prognosis, quality of life, cohort, study protocol

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Large multicenter prospective cohort study of NMIBC patients recruited shortly after diagnosis
- Extensive dietary, lifestyle, medical, and HRQOL data at multiple time points after diagnosis
- Availability of blood samples at 3 and 15 months after diagnosis, and formalin-fixed, paraffin-embedded tumour tissue
- Limited power for subgroup analyses
- Loss to follow-up potentially influencing validity of results

INTRODUCTION

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

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

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

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

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

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

METHODS AND ANALYSIS

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

Patient population

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

Patient and public involvement

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

Data collection and management

Questionnaires

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

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

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

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

HRQOL is assessed at all four time points with the validated European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 [31] and a 24-item module for patients with NMIBC, i.e. the EORTC QLQ-NMIBC24.[32] The EORTC QLQ-C30 contains five function scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, nausea, pain and vomiting) and six single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial impact), all scored from 1 (not at all) to 4 (very much)) and a global health status scale with ranges from 1 (very poor) to 7 (excellent). The EORTC QLQ-NMIBC24 contains six scales (urinary symptoms, malaise, future worries, bloating and flatulence, sexual function, and male sexual function) and five single items (intravesical treatment issues, sexual intimacy, risk of contaminating partner, sexual enjoyment, female sexual problems) scored from 1 (not at all) to 4 (very much). All scores will be linearly transformed to a 0 to 100 scale.

Furthermore, at T3mo patients are asked to report whether they are aware of possible risk factors for (bladder) cancer, received lifestyle advice from their physician, and what their attitudes are towards physicians giving lifestyle advice.

Table 1 Overview of data collection in UroLife at the four time points

	Included topics	T6wk	T3mo	T15mo	T51mo
Questionnaires					
Sociodemographic data	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			
Anthropometry	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
Lifestyle	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
Medical history	Previously diagnosed with cancer, family history of cancer	X			
	Comorbidities, medication use, dietary supplement use	X	X	X	X
Questions for females	Menstruation, menopause, use of contraceptives, use of hormone replacement therapy	X	X	X	X
	Pregnancy	X			
Diet	163- item Food Frequency Questionnaire	X	X	X	X
HRQOL	EORTC QLQ-C30 [31] and EORTC QLQ-NMIBC24 [32]	X	X	X	X
Awareness risk factors and lifestyle advice	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

Blood samples

Non-fasting blood samples are collected at T3mo and T15mo. At T3mo, 10 ml EDTA whole blood (for DNA isolation), 10 ml EDTA plasma and 10 ml heparin plasma is collected. At T15mo, 10 ml EDTA plasma and 10 ml heparin plasma is collected. Heparin plasma tubes are wrapped in aluminum foil to protect them from light. All blood samples are collected, processed and stored at -80°C locally in the participating hospitals according to a standard protocol before transportation on dry ice to the Radboud Biobank. The blood samples are stored in the Radboud Biobank at -80°C for future analyses of genetic and other biomarkers. Analysis of heparin plasma levels of nine biomarkers of fruit and vegetable consumption is planned. Concentration of six carotenoids (i.e. alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, lycopene and zeaxanthin), alpha-tocopherol, beta- and gamma-tocopherol and retinol were measured by HPLC (Thermo Scientific Accela LC system; Thermo Fisher Scientific) and analyzed by using ChromQuest 5.0, Version 3.2.1 software (Thermo Fisher Scientific).

Tumour samples

From patients diagnosed with T1 NMIBC, tumour specimens will be collected in two batches in 2019 and 2021. Tumour blocks will be identified by using the PALGA foundation and retrieved using the Dutch National Tissuebank Portal (DNTP) from the local pathology laboratories. Pathology review will be performed and tissue microarrays will be constructed. Molecular subtypes will be assessed by immunohistochemistry in 2021. As the development of a molecular classification system for NMIBC is still in progress and no consensus system is available yet,[33] we will use the most suitable evidence-based subtyping method that will then be available.

Clinical data

For all patients with NMIBC, information about disease characteristics and therapy for the initial tumour is collected from the medical records by data managers of the Netherlands

Cancer Registry. Information about tumour characteristics includes incidence date, clinical (cTNM) and post-surgical (pTNM) stage,[34] tumour grade, concomitant carcinoma in situ, multifocality, number of tumours and histology. With respect to therapy, information is collected on type of cystoscopy (white or blue light) and on transurethral resection (TUR), i.e. date of TUR, presence of detrusor in the surgical specimen, and presence of lymphovascular invasion. Furthermore, data on local treatment (e.g., intravesical chemotherapy, BCG) with start and stop dates and, if applicable, on cystectomy (e.g., date, type) are collected.

Data on clinical outcomes, i.e. recurrence and progression, with dates of diagnosis, tumour characteristics, and therapy is also collected from the medical records by data managers of the Netherlands Cancer Registry. Information on vital status is collected by linkage with the Personal Records Database. All patients will be followed for at least 5 years.

Power considerations & Data analysis

Risk of recurrence (or progression) will be evaluated as time to first recurrence (or progression). The association of pre- and post-diagnostic lifestyle factors, as well as changes in lifestyle factors, with risk of recurrence and progression will be evaluated by estimating hazard ratios and 95% confidence intervals using Cox proportional hazards regression analyses. All analyses will be adjusted for age, gender, tumour characteristics, and other known confounders. Analytical techniques for longitudinal data and multiple outcomes will also be explored and applied. Our power calculation is based on 1,100 patients who will be followed for five years. For comparing the highest (n=275) vs. lowest quartile (n=275) of a lifestyle factor (or vice versa), this study will be sufficiently powered (two-sided alpha=0.05, power 80%) to detect a hazard ratio of ≥1.5 or ≥1.3 (or ≤0.7 or ≤0.8) when assuming a five-year recurrence risk of 31% or 78%,[35] respectively.[36, 37] With an assumed loss to follow-up of 25% after five years, detectable hazard ratios will increase to ≥1.6 or ≥1.4 (or ≤0.6 or ≤0.7), respectively. Lower hazard ratios can be detected when lifestyle factors are modeled continuously.

The association of lifestyle factors with HRQOL will be evaluated using longitudinal mixed model analyses, taking into account the within-subject variation in lifestyle and HRQOL over time and the between-subject variation. All analyses will be adjusted for age, gender, tumour characteristics, and other known confounders. Since we expect that the between-subject variation in lifestyle and HRQOL will be much larger than the within-subject variation, most information will come from the association observed between subjects and not from the association observed within subjects over time, Therefore, our power calculation is based on a cross-sectional correlation at one time point. With 825 patients (assuming a loss to follow-up of 25%) and using 10 predictor variables, we have 80% power to detect a small correlation (Cohen's f^2 of 0.02).[38, 39] Power will be higher when using repeated measurements over time, especially when there is within-subject variation of lifestyle factors and HRQOL over time.

Cohort status

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

DISCUSSION

The UroLife study is one of the largest multicenter prospective cohort studies on lifestyle and NMIBC outcomes worldwide. UroLife will provide new and comprehensive insights into whether lifestyle habits (or habit changes) are related to NMIBC outcomes and HRQOL, and whether these relations differ by tumour stage and molecular subtype. Unique features of

UroLife are the recruitment of patients shortly after diagnosis, collection of extensive dietary, lifestyle, medical, and HRQOL data at multiple time points after diagnosis, collection of blood (for DNA and biomarker analysis), and the availability of tumour tissue samples (for molecular classification).

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

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

ETHICS AND DISSEMINATION

The study protocol has been approved by the Committee for Human Research region Arnhem-Nijmegen (CMO 2013-494). Patients who agree to participate in the study provide written informed consent. The findings from our cohort study will be disseminated through peer-reviewed scientific journals, and presentations at (inter)national scientific meetings. Patients will be informed about the progress and results of this study through biannual newsletters and through the website of the study (https://www.radboudumc.nl/trials/urolife) and of the bladder cancer patient association (https://www.blaasofnierkanker.nl/). Also, presentations will be given at contact days of the bladder cancer patient association.

DECLARATIONS

Authors' contributions

AV, LALMK, AJW, EK, and KKHA contributed to the conception and design of the study. AV provides overall study management and coordinates the project. EW has contributed and LdG contributes to data collection. LdG, EW and AV drafted the manuscript. All authors have critically read and revised the manuscript. All authors approved the final version of the manuscript.

Funding

This work was supported by Alpe d'HuZes/Dutch Cancer Society (KUN 2013-5926) and Dutch Cancer Society (Project no. 11179). Sponsors were not involved in the study design nor will they be in the collection, analysis, and interpretation of data, or in the publications that will result from this study.

Competing interests

The authors declare that they have no competing interests.

Availability of data and material

Data and material are not yet available since enrollment to the study is still ongoing and data collection has not been completed yet. After completion of data collection, data will be made available by the corresponding author upon reasonable request.

Acknowledgements

We are grateful to all the patients who participate in this study and we would like to thank the following hospitals for their involvement in recruitment for the UroLife study: Amphia Ziekenhuis, Breda/Oosterhout (Drs. D.K.E. van der Schoot); Ziekenhuis Bernhoven, Uden (Drs. A.Q.H.J. Niemer); Canisius-Wilhelmina Ziekenhuis, Nijmegen (Dr. D.M. Somford);

Catharina Ziekenhuis, Eindhoven (Dr. E.L. Koldewijn); Deventer Ziekenhuis, Deventer (Drs. P.L.M. van den Tillaar); Elkerliek Ziekenhuis, Helmond (Drs. E.W. Stapper †, Drs. P.J. van Hest); Gelre Ziekenhuizen, Apeldoorn/Zutphen (Drs. D.M. Bochove-Overgaauw); Isala Klinieken, Zwolle (Dr. E. te Slaa); Jeroen Bosch Ziekenhuis, 's-Hertogenbosch (Dr. J.R. Oddens; Dr. S. van der Meer); Meander Medisch Centrum, Amersfoort (Drs. F.S. van Rey); Medisch Spectrum Twente, Enschede (Dr. M. Asselman); Maxima Medisch Centrum, Veldhoven/Eindhoven (Dr. L.M.C.L. Fossion); Maasziekenhuis Pantein, Boxmeer (Drs. E. van Boven); Radboudumc, Nijmegen (Prof. Dr. J.A. Witjes); Rijnstate, Arnhem/Velp/Zevenaar (Drs. C.J. Wijburg); Slingeland Ziekenhuis, Doetinchem (Drs. A.D.H. Geboers); St. Anna Ziekenhuis, Geldrop (Drs. A. Sonneveld); Elisabeth-TweeSteden Ziekenhuis, Tilburg/Waalwijk (Dr. P.J.M. Kil); St. Jansdal Ziekenhuis, Harderwijk (Drs. W.J. Kniestedt); VieCuri, Venlo (Drs. G. Yurdakul, Dr. A.H.P. Meier); Ziekenhuis Gelderse Vallei, Ede (Drs. M.D.H. Kortleve); Ziekenhuisgroep Twente, Almelo/Hengelo (Dr. E.B. Cornel). In addition, we thank Ms. Monique Eijgenberger for her assistance in data collection. We also thank the data managers and research assistants of the Netherlands Cancer Registry held by the Netherlands Comprehensive Cancer Organisation (IKNL) for inviting patients and collecting the clinical data.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394-424.

2. Babjuk M, Böhle A, Burger M, et al. EAU guidelines on non–muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol* 2017;71(3):447-61.

3. Cambier S, Sylvester RJ, Collette L, et al. EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guerin. *Eur Urol* 2016;69(1):60-9.

4. Sievert KD, Amend B, Nagele U, et al. Economic aspects of bladder cancer: what are the benefits and costs? *World J Urol* 2009;27(3):295-300.

5. Schmidt S, Francés A, Garin JAL, et al. Quality of life in patients with non–muscle-invasive bladder cancer: One-year results of a multicentre prospective cohort study. *Urol Oncol* 2015;33(1):19.e7-19.e15.

6. Ligibel J. Lifestyle factors in cancer survivorship. *J Clin Oncol* 2012;30(30):3697-704.

7. Mehra K, Berkowitz A, Sanft T. Diet, Physical Activity, and Body Weight in Cancer Survivorship. *Med Clin North Am*. 2017;101(6):1151-65.

8. van Osch FH, Jochems SH, van Schooten F-J, et al. Quantified relations between exposure to tobacco smoking and bladder cancer risk: a meta-analysis of 89 observational studies. *Int J Epidemiol* 2016;45(3):857-70.

9. Cumberbatch MGK, Jubber I, Black PC, et al. Epidemiology of Bladder Cancer: A Systematic Review and Contemporary Update of Risk Factors in 2018. *Eur Urol* 2018;74(6):784-95.

10. Sun J-W, Zhao L-G, Yang Y, et al. Obesity and risk of bladder cancer: a dose-response meta-analysis of 15 cohort studies. *PloS one* 2015;10(3):e0119313.

11. Keimling M, Behrens G, Schmid D, et al. The association between physical activity and bladder cancer: systematic review and meta-analysis. *Br J Cancer* 2014;110(7):1862-70.

12. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018: Diet, nutrition, physical activity and bladder cancer. 2018, https://www.wcrf.org/dietandcancer

13. Crivelli JJ, Xylinas E, Kluth LA, et al. Effect of smoking on outcomes of urothelial carcinoma: a systematic review of the literature. *Eur Urol* 2014;65(4):742-54.

14. Hou L, Hong X, Dai M, et al. Association of smoking status with prognosis in bladder cancer: A meta-analysis. *Oncotarget* 2017;8(1):1278-89.

15. Westhoff E, Witjes JA, Fleshner NE, et al. Body Mass Index, Diet-Related Factors, and Bladder Cancer Prognosis: A Systematic Review and Meta-Analysis. *Bladder Cancer* 2018;4(1):91-112.

16. Kluth LA, Xylinas E, Crivelli JJ, et al. Obesity is associated with worse outcomes in patients with T1 high grade urothelial carcinoma of the bladder. *J Urol* 2013;190(2):480-6.

17. Wyszynski A, Tanyos SA, Rees JR, et al. Body mass and smoking are modifiable risk factors for recurrent bladder cancer. *Cancer* 2014;120(3):408-14.

18. Xu T, Zhu Z, Wang X, et al. Impact of body mass on recurrence and progression in Chinese patients with Ta, T1 urothelial bladder cancer. *Int Urol Nephrol* 2015;47(7):1135-41.

19. van der Heijden AG, Witjes JA. Recurrence, progression, and follow-up in non–muscle-invasive bladder cancer. *Eur Urol Suppl* 2009;8(7):556-62.

20. Sjödahl G, Lauss M, Lövgren K, et al. A molecular taxonomy for urothelial carcinoma. *Clin Cancer Res* 2012;18:3377-86.

21. Patschan O, Sjödahl G, Chebil G, et al. A molecular pathologic framework for risk stratification of stage T1 urothelial carcinoma. *Eur Urol* 2015;68(5):824-32.

22. Jung A, Nielsen ME, Crandell JL, et al. Quality of Life in Non-Muscle-Invasive Bladder Cancer Survivors: A Systematic Review. *Cancer Nurs* Published Online First: 1 June 2018. doi:10.1097/NCC.0000000000000606.

23. Mohamed N, Gilbert F, Lee C, et al. Pursuing Quality in the application of bladder Cancer quality of Life Research. *Bladder Cancer* 2016;2(2):139-49.

24. Gopalakrishna A, Longo TA, Fantony JJ, et al. Lifestyle factors and health-related quality of life in bladder cancer survivors: a systematic review. *J Cancer Surviv* 2016;10(5):874-82.

25. van de Poll-Franse LV, Horevoorts N, van Eenbergen M, et al. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. *Eur J Cancer* 2011;47(14):2188-94.

26. Wendel-Vos GW, Schuit AJ, Saris WH, et al. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol* 2003;56(12):1163-9.

27. de Hollander EL, Zwart L, de Vries SI, et al. The SQUASH was a more valid tool than the OBiN for categorizing adults according to the Dutch physical activity and the combined guideline. *J Clin Epidemiol* 2012;65(1):73-81.

28. Wagenmakers R, van den Akker-Scheek I, Groothoff JW, et al. Reliability and validity of the short questionnaire to assess health-enhancing physical activity (SQUASH) in patients after total hip arthroplasty. *BMC Musculoskelet Disord* 2008;9(1):141.

29. Siebelink E, Geelen A, de Vries JH. Self-reported energy intake by FFQ compared with actual energy intake to maintain body weight in 516 adults. *Br J Nutr* 2011;106(2):274-81.

30. NEVO-tabel (2011) Dutch Food Composition Database. Den Haag: RIVM/Voedingscentrum.

31. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85(5):365-76.

32. Blazeby JM, Hall E, Aaronson NK, et al. Validation and reliability testing of the EORTC QLQ-NMIBC24 questionnaire module to assess patient-reported outcomes in non-muscle-invasive bladder cancer. *Eur Urol* 2014;66(6):1148-56.

33. Chandrasekar T, Erlich A, Zlotta AR. Molecular Characterization of Bladder Cancer. *Curr Urol Rep* 2018;19(12):107.

34. Babjuk M, Böhle A, Burger M, et al. EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder: Update 2016. *Eur Urol* 2017;71(3):447-61.

35. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006;49(3):466-77.

36. Dupont WD, Plummer WD. Power and sample size calculations: a review and computer program. *Control Clin Trials* 1990;11(2):116-28.

37. Dupont WD, Plummer WD. PS: Power and Sample Size Calculation. http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize. Accessed 16 January 2019.

38. Faul F, Erdfelder E, Buchner A, et al. Statistical power analyses using G* Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods* 2009;41(4):1149-60.

39. Faul F, Erdfelder E, Buchner A, et al. G*Power: Statistical Power Analyses for Windows and Mac. http://www.gpower.hhu.de. Accessed 16 January 2019.

FIGURE LEGENDS

Figure 1 Timeline and study design of the UroLife study.

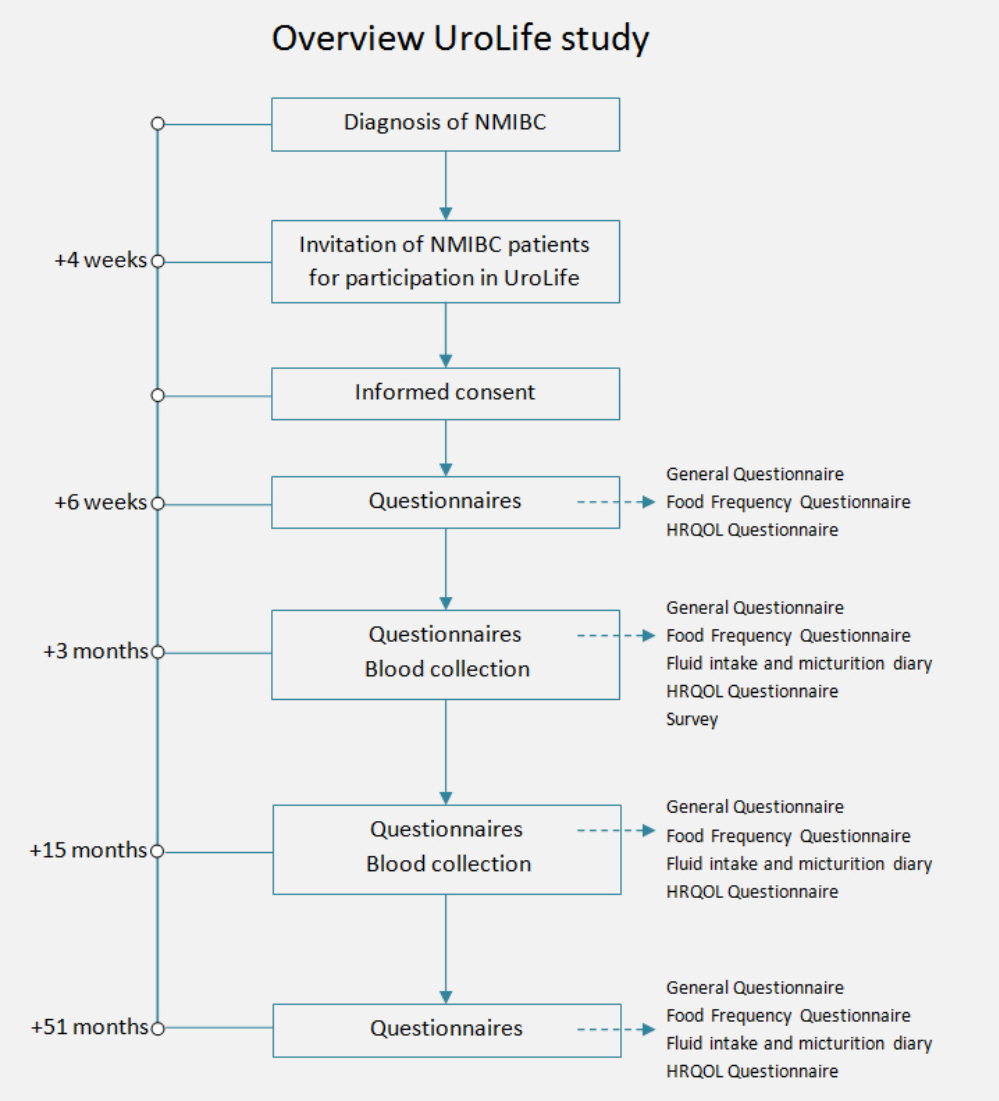

Figure 1 Timeline and study design of the UroLife study.

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030396.R2
Article Type:	Protocol
Date Submitted by the Author:	18-Sep-2019
Complete List of Authors:	de Goeij, Liesbeth; Radboudumc, Department for Health Evidence Westhoff, Ellen; Radboudumc, Department for Health Evidence Witjes, JA; Radboudumc, Department of Urology Aben, Katja; Netherlands Comprehensive Cancer Organisation; Radboudumc, Department for Health Evidence Kampman, Ellen; Wageningen University Kiemeney, Lambertus; Radboudumc, Department for Health Evidence Vrieling, Alina; Radboudumc, Department for Health Evidence
Primary Subject Heading:	Urology
Secondary Subject Heading:	Epidemiology
Keywords:	Urological tumours < ONCOLOGY, EPIDEMIOLOGY, NUTRITION & DIETETICS

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

Liesbeth de Goeij[a], Ellen Westhoff[a], J. Alfred Witjes[b], Katja K.H. Aben[a,c], Ellen Kampman[d], Lambertus A.L.M. Kiemeney[a,b], Alina Vrieling[a*]

[a] Radboud university medical center, Radboud Institute for Health Sciences, Nijmegen, The Netherlands

[b] Radboud University Nijmegen Medical Center, Department of Urology, Nijmegen, The Netherlands

[c] Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands

[d] Wageningen University, Division of Human Nutrition and Health, Wageningen, The Netherlands

***Corresponding author:** Dr. Alina Vrieling, Radboud university medical center, Department for Health Evidence (Mailbox 133), P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel: +31 24 3616944, Fax: +31 24 3613505, e-mail: Alina.Vrieling@radboudumc.nl

Word count: 3040

ABSTRACT

Introduction:

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

Methods and analysis:

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

Ethics and dissemination:

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

Keywords: bladder cancer, diet, lifestyle, biomarkers, recurrence, prognosis, quality of life, cohort, study protocol

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Large multicenter prospective cohort study of NMIBC patients recruited shortly after diagnosis
- Extensive dietary, lifestyle, medical, and HRQOL data at multiple time points after diagnosis
- Availability of blood samples at 3 and 15 months after diagnosis, and formalin-fixed, paraffin-embedded tumour tissue
- Limited power for subgroup analyses
- Loss to follow-up potentially influencing validity of results

INTRODUCTION

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

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

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

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

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

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

METHODS AND ANALYSIS

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

Patient population

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

Patient and public involvement

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

Data collection and management

Questionnaires

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

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

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

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

HRQOL is assessed at all four time points with the validated European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 [31] and a 24-item module for patients with NMIBC, i.e. the EORTC QLQ-NMIBC24.[32] The EORTC QLQ-C30 contains five function scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, nausea, pain and vomiting) and six single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial impact), all scored from 1 (not at all) to 4 (very much)) and a global health status scale with ranges from 1 (very poor) to 7 (excellent). The EORTC QLQ-NMIBC24 contains six scales (urinary symptoms, malaise, future worries, bloating and flatulence, sexual function, and male sexual function) and five single items (intravesical treatment issues, sexual intimacy, risk of contaminating partner, sexual enjoyment, female sexual problems) scored from 1 (not at all) to 4 (very much). All scores will be linearly transformed to a 0 to 100 scale.

Furthermore, at T3mo patients are asked to report whether they are aware of possible risk factors for (bladder) cancer, received lifestyle advice from their physician, and what their attitudes are towards physicians giving lifestyle advice.

Table 1 Overview of data collection in UroLife at the four time points

	Included topics	T6wk	T3mo	T15mo	T51mo
Questionnaires					
Sociodemographic data	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			
Anthropometry	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
Lifestyle	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
Medical history	Previously diagnosed with cancer, family history of cancer	X			
	Comorbidities, medication use, dietary supplement use	X	X	X	X
Questions for females	Menstruation, menopause, use of contraceptives, use of hormone replacement therapy	X	X	X	X
	Pregnancy	X			
Diet	163- item Food Frequency Questionnaire	X	X	X	X
HRQOL	EORTC QLQ-C30 [31] and EORTC QLQ-NMIBC24 [32]	X	X	X	X
Awareness risk factors and lifestyle advice	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

Blood samples

Non-fasting blood samples are collected at T3mo and T15mo. At T3mo, 10 ml EDTA whole blood (for DNA isolation), 10 ml EDTA plasma and 10 ml heparin plasma is collected. At T15mo, 10 ml EDTA plasma and 10 ml heparin plasma is collected. Heparin plasma tubes are wrapped in aluminum foil to protect them from light. All blood samples are collected, processed and stored at -80°C locally in the participating hospitals according to a standard protocol before transportation on dry ice to the Radboud Biobank. The blood samples are stored in the Radboud Biobank at -80°C for future analyses of genetic and other biomarkers. Analysis of heparin plasma levels of nine biomarkers of fruit and vegetable consumption is planned. Concentration of six carotenoids (i.e. alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, lycopene and zeaxanthin), alpha-tocopherol, beta- and gamma-tocopherol and retinol were measured by HPLC (Thermo Scientific Accela LC system; Thermo Fisher Scientific) and analyzed by using ChromQuest 5.0, Version 3.2.1 software (Thermo Fisher Scientific).

Tumour samples

From patients diagnosed with T1 NMIBC, tumour specimens will be collected in two batches in 2019 and 2021. Tumour blocks will be identified by using the PALGA foundation and retrieved using the Dutch National Tissuebank Portal (DNTP) from the local pathology laboratories. Pathology review will be performed and tissue microarrays will be constructed. Molecular subtypes will be assessed by immunohistochemistry in 2021. As the development of a molecular classification system for NMIBC is still in progress and no consensus system is available yet,[33] we will use the most suitable evidence-based subtyping method that will then be available.

Clinical data

For all patients with NMIBC, information about disease characteristics and therapy for the initial tumour is collected from the medical records by data managers of the Netherlands

Cancer Registry. Information about tumour characteristics includes incidence date, clinical (cTNM) and post-surgical (pTNM) stage,[34] tumour grade, concomitant carcinoma in situ, multifocality, number of tumours and histology. With respect to therapy, information is collected on type of cystoscopy (white or blue light) and on transurethral resection (TUR), i.e. date of TUR, presence of detrusor in the surgical specimen, and presence of lymphovascular invasion. Furthermore, data on local treatment (e.g., intravesical chemotherapy, BCG) with start and stop dates and, if applicable, on cystectomy (e.g., date, type) are collected.

Data on clinical outcomes, i.e. recurrence and progression, with dates of diagnosis, tumour characteristics, and therapy is also collected from the medical records by data managers of the Netherlands Cancer Registry. Information on vital status is collected by linkage with the Personal Records Database. All patients will be followed for at least 5 years.

Power considerations & Data analysis

Risk of recurrence (or progression) will be evaluated as time to first recurrence (or progression). The association of pre- and post-diagnostic lifestyle factors, as well as changes in lifestyle factors, with risk of recurrence and progression will be evaluated by estimating hazard ratios and 95% confidence intervals using Cox proportional hazards regression analyses. All analyses will be adjusted for age, gender, tumour characteristics, and other known confounders. Analytical techniques for longitudinal data and multiple outcomes will also be explored and applied. Our power calculation is based on 1,100 patients who will be followed for five years. For comparing the highest (n=275) vs. lowest quartile (n=275) of a lifestyle factor (or vice versa), this study will be sufficiently powered (two-sided alpha=0.05, power 80%) to detect a hazard ratio of ≥1.5 or ≥1.3 (or ≤0.7 or ≤0.8) when assuming a five-year recurrence risk of 31% or 78%,[35] respectively.[36, 37] With an assumed loss to follow-up of 25% after five years, detectable hazard ratios will increase to ≥1.6 or ≥1.4 (or ≤0.6 or ≤0.7), respectively. Lower hazard ratios can be detected when lifestyle factors are modeled continuously.

The association of lifestyle factors with HRQOL will be evaluated using longitudinal mixed model analyses, taking into account the within-subject variation in lifestyle and HRQOL over time and the between-subject variation. All analyses will be adjusted for age, gender, tumour characteristics, and other known confounders. Since we expect that the between-subject variation in lifestyle and HRQOL will be much larger than the within-subject variation, most information will come from the association observed between subjects and not from the association observed within subjects over time, Therefore, our power calculation is based on a cross-sectional correlation at one time point. With 825 patients (assuming a loss to follow-up of 25%) and using 10 predictor variables, we have 80% power to detect a small correlation (Cohen's f^2 of 0.02).[38, 39] Power will be higher when using repeated measurements over time, especially when there is within-subject variation of lifestyle factors and HRQOL over time.

Cohort status

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

DISCUSSION

The UroLife study is one of the largest multicenter prospective cohort studies on lifestyle and NMIBC outcomes worldwide. UroLife will provide new and comprehensive insights into whether lifestyle habits (or habit changes) are related to NMIBC outcomes and HRQOL, and whether these relations differ by tumour stage and molecular subtype. Unique features of

UroLife are the recruitment of patients shortly after diagnosis, collection of extensive dietary, lifestyle, medical, and HRQOL data at multiple time points after diagnosis, collection of blood (for DNA and biomarker analysis), and the availability of tumour tissue samples (for molecular classification).

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

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

ETHICS AND DISSEMINATION

The study protocol has been approved by the Committee for Human Research region Arnhem-Nijmegen (CMO 2013-494). Patients who agree to participate in the study provide written informed consent. The findings from our cohort study will be disseminated through peer-reviewed scientific journals, and presentations at (inter)national scientific meetings. Patients will be informed about the progress and results of this study through biannual newsletters and through the website of the study (https://www.radboudumc.nl/trials/urolife) and of the bladder cancer patient association (https://www.blaasofnierkanker.nl/). Also, presentations will be given at contact days of the bladder cancer patient association.

DECLARATIONS

Authors' contributions

AV, LALMK, AJW, EK, and KKHA contributed to the conception and design of the study. AV provides overall study management and coordinates the project. EW has contributed and LdG contributes to data collection. LdG, EW and AV drafted the manuscript. All authors have critically read and revised the manuscript. All authors approved the final version of the manuscript.

Funding

This work was supported by Alpe d'HuZes/Dutch Cancer Society (KUN 2013-5926) and Dutch Cancer Society (Project no. 11179). Sponsors were not involved in the study design nor will they be in the collection, analysis, and interpretation of data, or in the publications that will result from this study.

Competing interests

The authors declare that they have no competing interests.

Availability of data and material

Data and material are not yet available since enrollment to the study is still ongoing and data collection has not been completed yet. After completion of data collection, data will be made available by the corresponding author upon reasonable request.

Acknowledgements

We are grateful to all the patients who participate in this study and we would like to thank the following hospitals for their involvement in recruitment for the UroLife study: Amphia Ziekenhuis, Breda/Oosterhout (Drs. D.K.E. van der Schoot); Ziekenhuis Bernhoven, Uden (Drs. A.Q.H.J. Niemer); Canisius-Wilhelmina Ziekenhuis, Nijmegen (Dr. D.M. Somford);

Catharina Ziekenhuis, Eindhoven (Dr. E.L. Koldewijn); Deventer Ziekenhuis, Deventer (Drs. P.L.M. van den Tillaar); Elkerliek Ziekenhuis, Helmond (Drs. E.W. Stapper †, Drs. P.J. van Hest); Gelre Ziekenhuizen, Apeldoorn/Zutphen (Drs. D.M. Bochove-Overgaauw); Isala Klinieken, Zwolle (Dr. E. te Slaa); Jeroen Bosch Ziekenhuis, 's-Hertogenbosch (Dr. J.R. Oddens; Dr. S. van der Meer); Meander Medisch Centrum, Amersfoort (Drs. F.S. van Rey); Medisch Spectrum Twente, Enschede (Dr. M. Asselman); Maxima Medisch Centrum, Veldhoven/Eindhoven (Dr. L.M.C.L. Fossion); Maasziekenhuis Pantein, Boxmeer (Drs. E. van Boven); Radboudumc, Nijmegen (Prof. Dr. J.A. Witjes); Rijnstate, Arnhem/Velp/Zevenaar (Drs. C.J. Wijburg); Slingeland Ziekenhuis, Doetinchem (Drs. A.D.H. Geboers); St. Anna Ziekenhuis, Geldrop (Drs. A. Sonneveld); Elisabeth-TweeSteden Ziekenhuis, Tilburg/Waalwijk (Dr. P.J.M. Kil); St. Jansdal Ziekenhuis, Harderwijk (Drs. W.J. Kniestedt); VieCuri, Venlo (Drs. G. Yurdakul, Dr. A.H.P. Meier); Ziekenhuis Gelderse Vallei, Ede (Drs. M.D.H. Kortleve); Ziekenhuisgroep Twente, Almelo/Hengelo (Dr. E.B. Cornel). In addition, we thank Ms. Monique Eijgenberger for her assistance in data collection. We also thank the data managers and research assistants of the Netherlands Cancer Registry held by the Netherlands Comprehensive Cancer Organisation (IKNL) for inviting patients and collecting the clinical data.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394-424.

2. Babjuk M, Böhle A, Burger M, et al. EAU guidelines on non–muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol* 2017;71(3):447-61.

3. Cambier S, Sylvester RJ, Collette L, et al. EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guerin. *Eur Urol* 2016;69(1):60-9.

4. Sievert KD, Amend B, Nagele U, et al. Economic aspects of bladder cancer: what are the benefits and costs? *World J Urol* 2009;27(3):295-300.

5. Schmidt S, Francés A, Garin JAL, et al. Quality of life in patients with non–muscle-invasive bladder cancer: One-year results of a multicentre prospective cohort study. *Urol Oncol* 2015;33(1):19.e7-19.e15.

6. Ligibel J. Lifestyle factors in cancer survivorship. *J Clin Oncol* 2012;30(30):3697-704.

7. Mehra K, Berkowitz A, Sanft T. Diet, Physical Activity, and Body Weight in Cancer Survivorship. *Med Clin North Am*. 2017;101(6):1151-65.

8. van Osch FH, Jochems SH, van Schooten F-J, et al. Quantified relations between exposure to tobacco smoking and bladder cancer risk: a meta-analysis of 89 observational studies. *Int J Epidemiol* 2016;45(3):857-70.

9. Cumberbatch MGK, Jubber I, Black PC, et al. Epidemiology of Bladder Cancer: A Systematic Review and Contemporary Update of Risk Factors in 2018. *Eur Urol* 2018;74(6):784-95.

10. Sun J-W, Zhao L-G, Yang Y, et al. Obesity and risk of bladder cancer: a dose-response meta-analysis of 15 cohort studies. *PloS one* 2015;10(3):e0119313.

11. Keimling M, Behrens G, Schmid D, et al. The association between physical activity and bladder cancer: systematic review and meta-analysis. *Br J Cancer* 2014;110(7):1862-70.

12. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018: Diet, nutrition, physical activity and bladder cancer. 2018, https://www.wcrf.org/dietandcancer

13. Crivelli JJ, Xylinas E, Kluth LA, et al. Effect of smoking on outcomes of urothelial carcinoma: a systematic review of the literature. *Eur Urol* 2014;65(4):742-54.

14. Hou L, Hong X, Dai M, et al. Association of smoking status with prognosis in bladder cancer: A meta-analysis. *Oncotarget* 2017;8(1):1278-89.

15. Westhoff E, Witjes JA, Fleshner NE, et al. Body Mass Index, Diet-Related Factors, and Bladder Cancer Prognosis: A Systematic Review and Meta-Analysis. *Bladder Cancer* 2018;4(1):91-112.

16. Kluth LA, Xylinas E, Crivelli JJ, et al. Obesity is associated with worse outcomes in patients with T1 high grade urothelial carcinoma of the bladder. *J Urol* 2013;190(2):480-6.

17. Wyszynski A, Tanyos SA, Rees JR, et al. Body mass and smoking are modifiable risk factors for recurrent bladder cancer. *Cancer* 2014;120(3):408-14.

18. Xu T, Zhu Z, Wang X, et al. Impact of body mass on recurrence and progression in Chinese patients with Ta, T1 urothelial bladder cancer. *Int Urol Nephrol* 2015;47(7):1135-41.

19. van der Heijden AG, Witjes JA. Recurrence, progression, and follow-up in non–muscle-invasive bladder cancer. *Eur Urol Suppl* 2009;8(7):556-62.

20. Sjödahl G, Lauss M, Lövgren K, et al. A molecular taxonomy for urothelial carcinoma. *Clin Cancer Res* 2012;18:3377-86.

21. Patschan O, Sjödahl G, Chebil G, et al. A molecular pathologic framework for risk stratification of stage T1 urothelial carcinoma. *Eur Urol* 2015;68(5):824-32.

22. Jung A, Nielsen ME, Crandell JL, et al. Quality of Life in Non-Muscle-Invasive Bladder Cancer Survivors: A Systematic Review. *Cancer Nurs* Published Online First: 1 June 2018. doi:10.1097/NCC.0000000000000606.

23. Mohamed N, Gilbert F, Lee C, et al. Pursuing Quality in the application of bladder Cancer quality of Life Research. *Bladder Cancer* 2016;2(2):139-49.

24. Gopalakrishna A, Longo TA, Fantony JJ, et al. Lifestyle factors and health-related quality of life in bladder cancer survivors: a systematic review. *J Cancer Surviv* 2016;10(5):874-82.

25. van de Poll-Franse LV, Horevoorts N, van Eenbergen M, et al. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. *Eur J Cancer* 2011;47(14):2188-94.

26. Wendel-Vos GW, Schuit AJ, Saris WH, et al. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol* 2003;56(12):1163-9.

27. de Hollander EL, Zwart L, de Vries SI, et al. The SQUASH was a more valid tool than the OBiN for categorizing adults according to the Dutch physical activity and the combined guideline. *J Clin Epidemiol* 2012;65(1):73-81.

28. Wagenmakers R, van den Akker-Scheek I, Groothoff JW, et al. Reliability and validity of the short questionnaire to assess health-enhancing physical activity (SQUASH) in patients after total hip arthroplasty. *BMC Musculoskelet Disord* 2008;9(1):141.

29. Siebelink E, Geelen A, de Vries JH. Self-reported energy intake by FFQ compared with actual energy intake to maintain body weight in 516 adults. *Br J Nutr* 2011;106(2):274-81.

30. NEVO-tabel (2011) Dutch Food Composition Database. Den Haag: RIVM/Voedingscentrum.

31. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85(5):365-76.

32. Blazeby JM, Hall E, Aaronson NK, et al. Validation and reliability testing of the EORTC QLQ-NMIBC24 questionnaire module to assess patient-reported outcomes in non-muscle-invasive bladder cancer. *Eur Urol* 2014;66(6):1148-56.

33. Chandrasekar T, Erlich A, Zlotta AR. Molecular Characterization of Bladder Cancer. *Curr Urol Rep* 2018;19(12):107.

34. Babjuk M, Böhle A, Burger M, et al. EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder: Update 2016. *Eur Urol* 2017;71(3):447-61.

35. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006;49(3):466-77.

36. Dupont WD, Plummer WD. Power and sample size calculations: a review and computer program. *Control Clin Trials* 1990;11(2):116-28.

37. Dupont WD, Plummer WD. PS: Power and Sample Size Calculation. http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize. Accessed 16 January 2019.

38. Faul F, Erdfelder E, Buchner A, et al. Statistical power analyses using G* Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods* 2009;41(4):1149-60.

39. Faul F, Erdfelder E, Buchner A, et al. G*Power: Statistical Power Analyses for Windows and Mac. http://www.gpower.hhu.de. Accessed 16 January 2019.

FIGURE LEGENDS

Figure 1 Timeline and study design of the UroLife study.

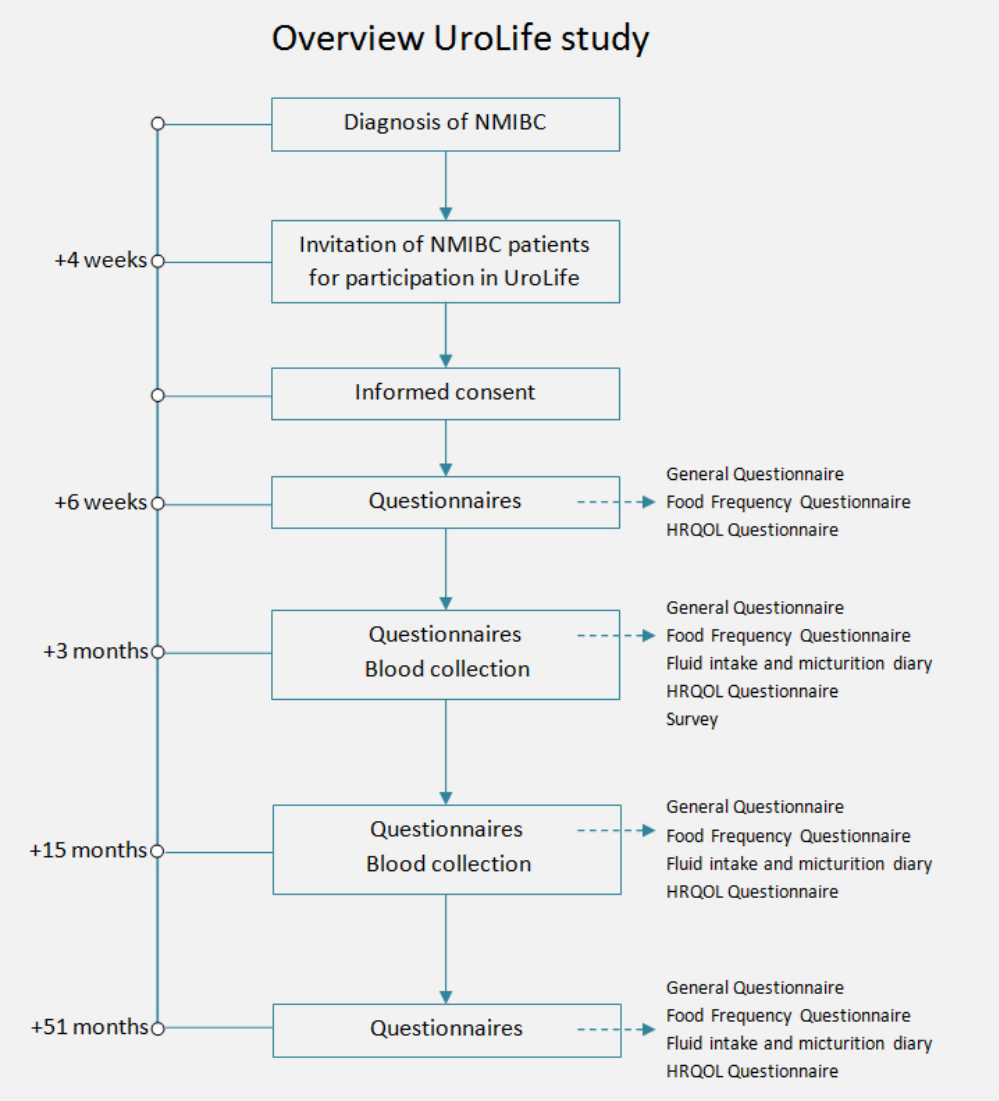

Figure 1 Timeline and study design of the UroLife study.