PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	de Goeij, Liesbeth; Westhoff, Ellen; Witjes, JA; Aben, Katja; Kampman, Ellen; Kiemeney, Lambertus; Vrieling, Alina

VERSION 1 – REVIEW

REVIEWER	Pierre Dugue Monash University, Australia
REVIEW RETURNED	06-May-2019

GENERAL COMMENTS	The study protocol is very clear, thorough and well written. I have only minor comments: 1) Why is the title about “dietary and lifestyle habits” but the rest of the paper, including UroLife acronym, not particularly focussing on diet? 2) Last paragraph of the Introduction is not very convincing, as it is unclear whether and how observing epidemiological associations about lifestyle may translate into personalised advice, or “enable patients to get some control over their own disease course”? 3) Is it possible to elaborate on the way information on recurrence and progression will be collected? 4) The collection of data at multiple time points is a great strength of the study – in this regard, the description “Analytical techniques for longitudinal data and multiple outcomes will also be considered” seems insufficient. 5) Virtually no consideration of potential biases is present in the Discussion 6) More details on ways or existing initiatives to provide personalized advice to cancer patients similar to the “ultimate aim” of the study would be interesting to the reader.

REVIEWER	Samantha Mason University of Leeds, UK
REVIEW RETURNED	21-May-2019

GENERAL COMMENTS	Very interesting study and really good explanation of method, power calculations and data analysis.

	A section about the aims and objectives of the research as well as outcomes, would improve the focus of the introduction. EORTC should be written in full the first time it is used in the paper. Urinary bladder cancer (UBC) is stated in the first sentence, but UBC isn't used again in the paper.

REVIEWER	Dr Ruth Conroy Consultant Clinical Oncologist The Christie NHS Foundation Trust UK
REVIEW RETURNED	23-Jul-2019

GENERAL COMMENTS	I think it's important to be clear in the abstract that analyses will be adjusted for tumour characteristics and other potential confounders. I think it's important to include patient dropout in the limitations as clearly this has been higher than expected (52% v 25%) and should also be mentioned in the analysis section.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
The study protocol is very clear, thorough and well written. I have only minor comments:

1) Why is the title about “dietary and lifestyle habits” but the rest of the paper, including UroLife acronym, not particularly focussing on diet?
We agree with the reviewer that we are not particularly focussing on diet in our study. Since dietary habits are part of lifestyle habits, we have now changed “dietary and lifestyle habits” to “lifestyle habits” in the title as well as in the text of the study protocol.

2) Last paragraph of the Introduction is not very convincing, as it is unclear whether and how observing epidemiological associations about lifestyle may translate into personalised advice, or “enable patients to get some control over their own disease course”?
The comment of the reviewer refers to the paragraph “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.” We agree that this has now been insufficiently described and is not fully clear. This part refers to our ultimate aim that, if we indeed find associations between lifestyle and prognosis that are confirmed by other epidemiological studies or randomized trials, lifestyle recommendations can be developed and personalized evidence-based lifestyle advice can be provided to patients with NMIBC, also according to tumour stage and molecular subtype, to enable them to have an influence on their clinical outcome. We have now left out this part in the introduction but provide more information in the Discussion, also answering to comment 6 of the reviewer.

3) Is it possible to elaborate on the way information on recurrence and progression will be collected?
We have now added the following information to make the collection of information on recurrence and progression more clear, and also added the collection of information on vital status:

Line 230-233: “Data on clinical outcomes, i.e. recurrence and progression, with dates of diagnosis, tumour characteristics, and treatment, 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."

4) The collection of data at multiple time points is a great strength of the study – in this regard, the description "Analytical techniques for longitudinal data and multiple outcomes will also be considered" seems insufficient.
We agree with the reviewer that this description may seem insufficient. However, several statistical approaches to deal with these type of data exist, and this research field is still very much in development (see e.g. review https://www.ncbi.nlm.nih.gov/pubmed/29389664). Therefore, at this stage we will provide no further specification, but we will explore and decide which approach will be most suitable to apply to our data at a later stage during this project, when we will actually start with our statistical analyses. To make more clear that we will take into account the data at multiple time points, we have now rephrased this part on analyses as:

Line 236-242: "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."

5) Virtually no consideration of potential biases is present in the Discussion.
We have now adjusted and extended the information on potential biases in the Discussion section:

Line 282-284: "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 the reliance on recall and self-report, or due to missing data, may be another potential limitation."

6) More details on ways or existing initiatives to provide personalized advice to cancer patients similar to the "ultimate aim" of the study would be interesting to the reader.
We have now extended this part of the Discussion:

Line 288-295: "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."

Reviewer #2:

Very interesting study and really good explanation of method, power calculations and data analysis.

A section about the aims and objectives of the research as well as outcomes, would improve the focus of the introduction.
We thank the reviewer for this advice. We have now rephrased the last paragraph of the introduction so it is formulated as an aim:

Line 112-116: "The aim of our study is to evaluate the association of pre- and postdiagnosis 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."

EORTC should be written in full the first time it is used in the paper.
We have changed EORTC into European Organisation for Research and Treatment of Cancer (EORTC) the first time it is used.

Urinary bladder cancer (UBC) is stated in the first sentence, but UBC isn't used again in the paper.
We have now removed this abbreviation in the first sentence of the protocol.

Reviewer #3:

I think it's important to be clear in the abstract that analyses will be adjusted for tumour characteristics and other potential confounders.

We have now added the following sentence to the abstract:
Line 40-42: "Statistical analyses will be adjusted for age, gender, tumour characteristics, and other known confounders."

I think it's important to include patient dropout in the limitations as clearly this has been higher than expected (52% v 25%) and should also be mentioned in the analysis section.

We would like to point out that loss to follow-up is not higher than expected: The response rate in our study was 52% (number of patients who participated in our study divided by the number of patients that were invited to participate in our study). The expected loss to follow-up is 25% and refers to the patients who did not fill in the follow-up questionnaires. Loss to follow-up has already been included as a limitation in the Discussion section, and the assumed loss to follow-up of 25% has been mentioned in the analysis section. We have now added the following information to the Strengths and limitations of this study:

Line 62: "Loss to follow-up potentially influencing validity of results"

VERSION 2 – REVIEW

REVIEWER	samantha mason University of Leeds, United Kingdom
REVIEW RETURNED	14-Sep-2019

GENERAL COMMENTS	Very interesting study design. Clearly written and presented.

REVIEWER	Dr Ruth Conroy The Christie NHS Foundation Trust UK
REVIEW RETURNED	02-Sep-2019

GENERAL COMMENTS	Analytical techniques for longitudinal data and multiple outcomes will also be explored and applied - I think it would be much better if the techniques were determined at the outset. Otherwise I think the changes made mean it is suitable for publication.

VERSION 2 – AUTHOR RESPONSE

Reviewer 3

we would like to refer to our previous rebuttal, in which we stated: "Several statistical approaches to deal with these type of data exist, and this research field is still very much in development (see e.g. review https://www.ncbi.nlm.nih.gov/pubmed/29389664). Therefore, at this stage we will provide no further specification, but we will explore and decide which approach will be most suitable to apply to our data at a later stage during this project, when we will actually start with our statistical analyses."