PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Attitude toward active surveillance: a cross-sectional survey among uro-andrological patients
AUTHORS	Capogrosso, Paolo; Boeri, Luca; Ventimiglia, Eugenio; Camozzi, Ilenya; Cazzaniga, Walter; Chierigo, Francesco; Scano, Roberta; Briganti, A; Montorsi, Francesco; Salonia, Andrea

VERSION 1 – REVIEW

REVIEWER	Simon Kim Case Western Reserve University, US
REVIEW RETURNED	17-Mar-2018

GENERAL COMMENTS	Thank you for the opportunity to review this study on the patient attitudes towards active surveillance. This is an intriguing study with some important implications about increasing acceptability of active surveillance for indolent cancer. I had several questions for the authors. First, in the survey studies, the authors should report the response rate. Low response rates introduce selection bias, but that does not appear to be case here. Second, the authors need to detail the methodology of the survey in their study. For example, did the authors conduct focus groups for patient and conduct a pilot survey to test each survey item. I am also concerned that the survey does not appropriately describe active surveillance prior to assessing patient attitudes. Active surveillance is a disease management strategy among malignancies that are indolent and where overtreatment is a common concern. One could criticize the current survey in that it does not allow patients to contextualize active surveillance. Third, the authors need to better clarify the reasoning behind the survey selection. For instance, why did the authors include younger patients (< 50 years old) in the survey sample? There are few clinical situations where active surveillance are germane to this patient population. While the authors present patient age as an important factor in the acceptance of active surveillance, one could plausibly argue that this is not a clinically important finding or will not change clinical practice. Fourth, I think the one area the authors understate is the inclusion of cancer patients (prostate and kidney cancer). I would suggest the authors perform a subgroup analysis of these patients to assess if their views differed compared to the other patients. Moreover, the authors need describe the stages and treatments of the kidney and

	prostate cancer patients. These are important findings since the type of GU cancer (kidney vs. prostate) and stage may be important confounders in the results. Fifth, the discussion section, though well written, would be better served if the authors suggest what are the next steps to promote patient acceptability of active surveillance (interventions, education, etc.)

REVIEWER	Ahmad Algohary Case Western Reserve University, Cleveland, Oh, USA
REVIEW RETURNED	25-Apr-2018

GENERAL COMMENTS	This study investigates the patients' attitude toward Active Surveillance at their first clinical assessment for uro-andrological disorders. Some questions/comments: 1- Some abbreviations are used without being established first. 2- Authors just mentioned the overall level of education for patients, but never mentioned their level of education about Active Surveillance. This could affect the results and especially the acceptance rate of AS significantly. 3- In discussion, literature regarding PCa was covered but never the other types of disorders that were investigated at the first place. 4- The cohort is not gender balanced. How did you address the unbalanced cohort issue in your analysis ?

VERSION 1 – AUTHOR RESPONSE

Reviewer#1

Q1: First, in the survey studies, the authors should report the response rate. Low response rates introduce selection bias, but that does not appear to be case here.

A1: We thank you the Reviewer#1 for this comment**.** As for the specific suggestion, we have modified the text reporting the actual response rate. Overall, we had a 51% response rate: this may have introduced a selection bias; however, in order to try and reduce the overall impact of a specific bias, we compared responders and non responders and we did not find any difference in terms of socio-demographic characteristics between patients who did complete and those who did not complete the whole survey at a sensitivity analysis (all $p>0.05$).

Q2: Second, the authors need to detail the methodology of the survey in their study. For example, did the authors conduct focus groups for patient and conduct a pilot survey to test each survey item. I am also concerned that the survey does not appropriately describe active surveillance prior to assessing patient attitudes. Active surveillance is a disease management strategy among malignancies that are indolent and where overtreatment is a common concern. One could criticize the current survey in that it does not allow patients to contextualize active surveillance.

A2: We respectfully only partially agree with the Reviewer#1 for this very relevant comment. We are aware of the limitation of using a non-validated questionnaire without conducting a pilot survey. However, we have developed this questionnaire in collaboration with an expert in sociology and human behaviour exactly to address the various issues in a non-focus group context. In this context,

for instance, as reported in the Appendix 1, the question n.7 was carefully developed to underline the concept of *"leaving untreated an indolent cancer"* [If you were diagnosed with an urological cancer (e.g. prostate, kidney) that could be left untreated, would you be willing to follow-up the disease with both invasive (e.g. biopsies) and non-invasive tests without undergoing any active treatment?]

As a whole, although we are absolutely aware of the possible inaccuracies and biases deriving from the specific nature of the questions and the context (outpatients) where the questionnaire had been administered, we believe that those closed questions were able to properly capture patients' opinion on AS.

Q3: Third, the authors need to better clarify the reasoning behind the survey selection. For instance, why did the authors include younger patients (< 50 years old) in the survey sample? There are few clinical situations where active surveillance are germane to this patient population. While the authors present patient age as an important factor in the acceptance of active surveillance, one could plausibly argue that this is not a clinically important finding or will not change clinical practice.

A3: We thank the Reviewer#1 for this comment. However, we respectfully disagree with the concept that age per se did not represent a significant aspect and that enrolling even a cohort of young patients was of importance; indeed, from a demographic standpoint, patients presenting for prostate cancer are younger and younger on a yearly basis, thus outlining the importance of informing them comprehensively even in terms of sexual and reproductive issues and sequelae potentially associated to every curative approach (see, in this context, J Sex Med. 2017 Mar;14(3):285-296 and Fertil Steril. 2013 Aug;100(2):367-72.e1). More specifically, median age in our study was 40 years, with one out of three patients having more than 55 years. The younger age may have even strengthen our results since we provided novel findings about patients' opinion on AS in a relatively young population, thus encouraging physicians to discuss surveillance management even in younger patients with cancer diagnosis in the everyday clinical setting.
This aspect has been better pointed out throughout the Discussion section of the manuscript.

We chose to perform our survey on a population of patients visiting the outpatient clinic of our institute for uro-andrological purpose. In the majority of cases, patients were assessed for benign disorders: as such, it is likely that most of them had not previously discussed about cancer surveillance and cancer treatment complications, thus providing virtually unbiased information of their opinion toward AS.

Q4: Fourth, I think the one area the authors understate is the inclusion of cancer patients (prostate and kidney cancer). I would suggest the authors perform a subgroup analysis of these patients to assess if their views differed compared to the other patients. Moreover, the authors need describe the stages and treatments of the kidney and prostate cancer patients. These are important findings since the type of GU cancer (kidney vs. prostate) and stage may be important confounders in the results.

A4: We agree with the Reviewer#1 comments. Indeed, we have analyzed data from the specific subcohort of patients with a diagnosis of cancer within our cohort without finding any difference in terms of attitudes toward AS compared to non-cancer patients; moreover, seeking medical help for cancer was not associated with a specific attitude toward AS at multivariable analyses. Given the low number of patients diagnosed with cancer, we did not reach power enough to detect a difference between kidney and prostate cancer patients. Moreover, as for the design of the study, clinical data, thus including cancer stage and disease risk were not collected.

Q5: Fifth, the discussion section, though well written, would be better served if the authors suggest what are the next steps to promote patient acceptability of active surveillance (interventions,

education, etc.).

A5: We thank the Reviewer#1 for this very proactive comment. To this aim, we have modified the Discussion section accordingly. The new version reads as follows: "…These results encourage physicians to comprehensively discuss cancer surveillance with younger patients who might be less inclined to accept this type of management, thus stressing the importance of a proper counselling aimed to improve the value of patients understanding and consciousness about treatment options, by giving a reliable estimation of the risks and side effects associated with both surveillance protocols and active treatments, both in oncologic and functional terms. In this context, to further stress the relevance of a fruitful interaction with the patients, every physician should provide the outcomes of the treating center along with those published across the scientific literature, thus to limiting and avoid false expectations…**."**

Reviewer#2

Q1: Some abbreviations are used without being established first.

A1: We have revised the text accordingly.

Q2: Authors just mentioned the overall level of education for patients, but never mentioned their level of education about Active Surveillance. This could affect the results and especially the acceptance rate of AS significantly.

A2: We partially agree with the comment of the Reviewer#2. We have developed a specific questionnaire, in collaboration with an expert in sociology and human behavior, to assess an unbiased patient' opinion on AS. As reported in the Appendix 1, the question n.7 was carefully developed to underline the concept of *"leaving untreated an indolent cancer"* and managed the disease with both invasive and non-invasive tests. [If you were diagnosed with an urological cancer (e.g. prostate, kidney) that could be left untreated, would you be willing to follow-up the disease with both invasive (e.g. biopsies) and non-invasive tests without undergoing any active treatment?]

We believe this closed question was able to properly capture the baseline patients' awareness on the topic of AS. Likewise, although education status could be eventually of relevance, we believe that education status and actual education on AS could be completely separated from each other.

Q3: In discussion, literature regarding PCa was covered but never the other types of disorders that were investigated at the first place.

A3: We completely agree with the Reviewer#2. Indeed, still there is a huge lack of data on patients' attitude toward kidney cancer surveillance management. Thereof, we have underlined the lack of relevant data on patients' compliance toward surveillance for kidney cancer in the discussion section.

Q4: The cohort is not gender balanced. How did you address the unbalanced cohort issue in your analysis ?

A4: We were not able to balance our cohort according to gender since we relied on a population of patients seeking medical help at the uro-andrological outpatient clinic of our center; as such, it was expected that a significantly higher number of male patients would be included. However, a 20% of female subjects participated to the survey and we observed a significant difference in the opinion toward AS according to gender, thus suggesting that an adequate number of female patients had been included in the study. A further potential bias has been added to the Discussion section, accordingly.

VERSION 2 – REVIEW

REVIEWER	Simon Kim University Hospitals, United States
REVIEW RETURNED	11-Jul-2018

GENERAL COMMENTS	The authors have sufficiently answered the comments.