

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Protocol for a Canadian Prospective Observational Study of Decision-making on Active Surveillance or Surgery for Low Risk Papillary Thyroid Cancer
AUTHORS	Sawka, Anna; Ghai, Sangeet; Tomlinson, George; Rotstein, Lorne; Gilbert, Ralph; Gullane, Patrick; Pasternak, Jesse; Brown, Dale; de Almeida, John; Irish, Jonathan; Chepeha, Douglas; Higgins, Kevin; Monteiro, Eric; Jones, J; GAFNI, Amiram; Goldstein, David

VERSION 1 – REVIEW

REVIEWER	Megan Haymart, MD University of Michigan, Ann Arbor, MI
REVIEW RETURNED	10-Nov-2017

GENERAL COMMENTS	The authors provided details on a protocol to assess active surveillance versus surgery for low-risk papillary thyroid cancer. This is a timely and pertinent research topic. The manuscript is well-written and the protocol is described in detail. A strength of this particular protocol is the addition of the secondary outcomes: rationale for decision, role of patient in the decision, and decision satisfaction. My only concern is feasibility. Can the authors provide estimates on intended enrollment number? Do they have pilot data suggesting that an adequate number of patients in their catchment area would be interested in active surveillance?
-------------------------	---

REVIEWER	R Michcael Tuttle Memorial Sloan Kettering Cancer Center New York, New York USA
REVIEW RETURNED	26-Dec-2017

GENERAL COMMENTS	Well written description of an important prospective study. I have only one comment to consider, in Table 2, a confirmed increase in size of > 3mm is an indication to move to salvage surgery. Now that we understand that some of these very low risk papillary thyroid cancers can grow very slowly over many years, should we consider adding a time variable to the 3 mm cut off. For example, if a tumor grew 3 mm over 10 years, but was still confined to the thyroid and have no evidence of metastasis, would surgery still be required?
-------------------------	--

VERSION 1 – AUTHOR RESPONSE

Anna M. Sawka, MD, PhD, FRCPC

Responses to the Editor and Reviewers

Response to the Editor and Editorial Staff:

We are thankful to the Editor for the opportunity to revise this manuscript. The following Editorial Requirement has been requested, “Please revise your title to state the research question, study design, and setting (location). This is the preferred format for the journal”.

1) In response to this request, we have revised the title as follows (shown on page 1 of the revised manuscript): “A Protocol for a Canadian Prospective Observational Study of Decision-making on Active Surveillance or Surgery for Low Risk Papillary Thyroid Cancer”

We have also made the following changes, in response to editorial requests on January 11 and 12, 2018:

- 1) Both clean and changes highlighted versions of the manuscript are submitted.
- 2) The strengths and limitations section following the Abstract has been re-formatted in keeping with the editorial recommendations (4 bulleted statements directly relating to the study)
- 3) Reference 37, which was cited in a Table, but was not essential, was removed.

Response to Reviewer #1:

We are grateful to the Reviewer for the careful review. We appreciate the positive feedback on this research area being timely and pertinent as well as the strength of the inclusion of the secondary outcomes.

1) The Reviewer has raised concerns about feasibility of participant recruitment for this study and inquired if we may have pilot data. At the time of initiation of this study, although we were aware that University Health Network is a high volume thyroid surgical center in the largest city in Canada, with the highest incidence rate of thyroid cancer, we did not have any pilot data suggesting that patients or their physicians would be interested in active surveillance of low risk papillary thyroid cancer. In fact, as the Reviewer has correctly pointed out, there were potential concerns about lack of interest in active surveillance. For example, our group surveyed Canadian Otolaryngology/Head and Neck Surgeons and Endocrinologists on disease management recommendations of papillary microcarcinoma, and in the case of a hypothetical patient with a solitary 8mm papillary thyroid cancer (in absence of any other adverse features nor family history nor radiation exposure), only 2% of the 113 respondents recommended active surveillance without surgery (Merdad M, Eskander A, De Almeida J, Freeman J, Rotstein L, Ezzat S, Sawka AM, Goldstein DP. Current management of papillary thyroid microcarcinoma in Canada. *J Otolaryngol Head Neck Surg.* 2014 ;43:32). In the mean time, in clinical practice, we observed that some patients were inquiring about reports of active surveillance from Japan, in hopes of avoiding thyroid surgery. Yet there was no active surveillance study for low risk thyroid cancer available to such patients in Canada. Some patients expressed frustration about having to travel to other countries, to participate in active surveillance research in this area. Still, we did not have a clear understanding of how often low risk papillary thyroid cancer patients would choose active surveillance over surgery, IF they were given this choice (which they typically were not). Given this uncertainty, we were careful in the design of the study, to ensure inclusion of a first phase, prospectively examining how often patients choose active surveillance or surgery, respectively, and why. This is a descriptive study and an a priori defined sample size is not required; in particular we have made no specific requirement for the number of patients choosing active surveillance (which we planned not to control) as that is the foundation of our research question. Furthermore, in the second phase of the study, we were careful to design the study as two

single arm prospective studies (ie. active surveillance or surgery, respectively), such that respective descriptive data could be reported, if the target sample size of 200 patients (in total from active surveillance and surgical arms) could not be achieved, or if the distribution was such that a statistical comparison was inappropriate. We will stop recruiting patients in the first phase of the study (deciding on disease management) once the target recruitment of 200 patients is achieved in total in the follow-up study (combined number of patients in the surgery and active surveillance follow-up groups). In our registered protocol, we have indicated that our estimated completion data (ie. completion of recruitment and at least 1 year of follow-up) is May of 2026 (10 years after initiation of the study). Thus, a relatively low recruitment target of at least 22 patients per year (for 9 years) is needed, and at present, this rate is being far exceeded. The long time frame of this study, will also enable longer, more clinically meaningful, follow-up for those who are recruited in the early years, but still allow for earlier reporting of the initial decision and 1 year follow-up results, depending on early recruitment success. We have clarified the recruitment plan in the first paragraph on page 12 and acknowledged the Reviewers' concern about recruitment feasibility on page 14 under Recruitment and Status of the Study.

Response to Reviewer #2

We appreciate the Reviewer's thoughtful review. We also appreciate the positive comments about writing of the manuscript and the importance of the study.

1) The Reviewer has questioned whether a time period cut-off should be added to the primary tumor growth criterion for salvage surgery. The Reviewer has provided the hypothetical example of a tumor growing "3 mm over 10 years" (but still confined to the thyroid with no metastases), and inquired whether surgery would still be required. This is an excellent question, which is impossible to answer based on currently available data in the literature. In the field of thyroid cancer, although we are familiar with the importance of time-based measures for biochemical measures (eg. doubling times of biochemical markers), we are not aware of a precedent for thyroid cancer structural imaging findings. Furthermore, there is really no published 10 year follow-up data available for active surveillance of primary tumors >1cm in diameter, which are included in this study, so it is not possible to know how often the situation in question would occur. Potential factors which could impact interpretation of time-based imaging changes could include: the biological behaviour of the tumor, the error in the measurement, the timing of scheduled follow-up imaging (which may be different in the early years compared to later years for stable disease), the overall duration of follow-up, and possibly the timing of when a structural change may be most likely to occur (if the risk different over time e.g. early progression more likely). Many of these variables are currently unknown in this field. With respect to the specific example give by the reviewre, it is important to note that our criterion for surgery is >3mm growth of the primary tumor (demonstrated on two consecutive ultrasounds), so technically, a tumor that has grown 3mm and not more than that (in absence of metastatic disease or encroachment on critical structures), would NOT meet our criteria for salvage surgery (unless the patient wanted it), regardless of the time point. The Reviewer's comment highlights the importance of long-term follow-up in prospective research on management of low risk papillary thyroid cancer, and, as we indicated in our response to Reviewer 1, this is an issue that we are very aware of, so have planned a 10 year time frame for our study. If we are able to sustain funding for the study, even longer prospective follow-up would be ideal. The only way to answer the Reviewer's important question is by execution of such research. In response to the Reviewer's thought-provoking comment, we have added a statement on the importance of long-term follow-up in such research, in the final concluding section of the manuscript (page 15, Perspective section). Although we will not change our criteria for salvage surgery, it would be interesting to explore a response Reviewer's question in the future. We thank the Reviewer for this very interesting suggestion.

VERSION 2 – REVIEW

REVIEWER	Megan Haymart, MD University of Michigan, USA
REVIEW RETURNED	19-Jan-2018

GENERAL COMMENTS	The authors addressed all concerns.
-------------------------	-------------------------------------

REVIEWER	R Michael Tuttle Memorial Sloan Kettering Cancer Center
REVIEW RETURNED	07-Feb-2018

GENERAL COMMENTS	The authors present their well thought out and developed protocol for an observational study of low risk papillary thyroid cancers being followed in Canada. In addition to examining the standard oncologic endpoint (disease progression), they are also studying important aspects of decision making and decision satisfaction. Understanding the decision making process in this clinical situation is very important and has not been studied. The manuscript is well written and I don't have any suggestions for improvement.
-------------------------	---