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Deciding on Active Surveillance or Surgery for Primary Management of Low Risk Papillary Thyroid Cancer: Study Protocol for a Prospective Observational Study

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Manuscripts

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3 **Deciding on Active Surveillance or Surgery for**
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6 **Primary Management of Low Risk Papillary Thyroid Cancer:**
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9 **Study Protocol for a Prospective Observational Study**
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ABSTRACT

Introduction Low risk papillary thyroid cancer (PTC) is increasingly being diagnosed throughout the world; yet the mortality risk is low compared to other malignancies.

Traditional management includes thyroid surgery, sometimes followed by radioactive iodine and thyroid hormone treatment. Active surveillance (AS) has been proposed as a means to reduce over treatment of PTC. AS involves close disease follow-up, with the intention to intervene if the disease progresses, or upon patient request.

Methods and analysis This is a multi-phase prospective observational study. In the first phase of this study, consenting eligible adults with low risk PTC that is < 2cm in maximal diameter, confined to the thyroid, and not immediately adjacent to critical structures in the neck, are provided verbal and written information about PTC disease prognosis following surgery or AS. Questionnaires are administered at baseline and after the disease management decision on AS or surgery is finalized. Patients may choose either option (surgery or AS), and the primary outcome is the frequency with which either disease management option is chosen. Secondary outcomes include: rationale for the decision, role of the patient in decision-making, and decision satisfaction.

In the second phase of the study, consenting eligible adult patients who completed the first study phase may enroll in respective AS or surgery group follow-up studies. The following outcomes are examined 1 year after enrollment in the follow-up phase: decision regret about disease management choice (primary outcome), psychological distress, disease-specific quality of life, fear of disease progression, body image

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3 satisfaction, disease progression, cross-over to surgery in the AS group, new chronic
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5 thyroid hormone use, and healthcare resource utilization.
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9 **Ethics and dissemination** The University Health Network Research Ethics Board
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11 approved this study (ID 15-8942). The results will be published in an open access
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13 journal.
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17 **Registration details** Clinicaltrials.gov: NCT03271892

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19 (<https://clinicaltrials.gov/ct2/show/NCT03271892?term=NCT03271892&cond=Thyroid+Cancer%2C+Papillary&cntry1=NA%3ACA&rank=1>)
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28 **Strengths and limitations of this study**

29 **Strengths**

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- This is the first study to conduct a detailed prospective evaluation of decision-making related to the choice of active surveillance (AS) or immediate thyroid surgery, for management of low risk papillary thyroid cancer (PTC).
 - All patients being considered for enrollment must have cytopathological confirmation of the diagnosis of PTC or “suspicious for PTC” with review or relevant neck imaging by an experienced study radiologist +/- experienced thyroid surgeon.
 - This is a prospective study.
 - This study is not funded by industry.

43 **Limitations**

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- This study is not randomized. However, by enabling patients to choose their disease management strategy, our study will inform the understanding of decision-making process of patients with low risk PTC considering the choice of AS or surgery.
 - For patients who undergo thyroid cancer surgery, the surgical procedure and associated follow-up procedures will be at the discretion of the treating physician and patient; surgery is not restricted to be performed in the study centre. The surgical group is intended to reflect usual care and medical records of thyroid cancer-related care will be reviewed.

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3 Increased utilization of diagnostic imaging has resulted in increased diagnosis of
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5 incidental malignancies that have a low risk of progression or death.¹ Some recent
6
7 annual estimates on the number of individuals newly diagnosed with thyroid cancer
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9 include: 298,000 world-wide², 7,100 in Canada³, 56,870 in the United States⁴, 53,000 in
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11 Europe⁵, and 3,400 in the United Kingdom². In Canada, TC incidence is rising faster
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13 than any other malignancy³, with an increase of 156% from 1991 to 2006⁶. The survival
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15 rate of thyroid cancer is among the highest of all malignancies^{3,4} and the 5-year survival
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17 rate for early stage (local) thyroid cancer is reported to be >99%⁴. Most of the increase
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19 in thyroid cancer incidence is attributed to detection of papillary thyroid cancer (PTC) ≤
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21 2cm in diameter⁷⁻¹¹, especially, localized disease without metastases (i.e. no spread of
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23 disease beyond the thyroid)^{8,11,12}. PTCs ≤2 cm in diameter are estimated to account for
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25 60-68% of new cases^{7,9}. Thyroid cancer treatment traditionally involves thyroid surgery,
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27 which may be followed by thyroid hormone replacement (lifelong) and radioactive iodine
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29 treatment¹³⁻¹⁵. However, treatment-related morbidity in individuals at low risk of dying
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31 from their disease is a relevant concern; thus the consideration of an option for a
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33 conservative, non-operative management approach for select to low risk PTC cases,
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35 has been proposed by some experts¹⁶⁻¹⁸.

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37 Active surveillance (AS) of a malignancy consists of close clinical/diagnostic test follow-
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39 up (in lieu of immediate surgery), with the intention of treatment with curative intent if the
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41 disease progresses or the patient requests it. In two recent prospective observational
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43 studies from Japan, patients with PTC ≤1cm in diameter underwent AS and there were
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45 no TC-related deaths, no distant metastatic recurrences, and the rate of cervical lymph
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47 node recurrence was approximately 1 to 2% (followed on average for 5-6 years)^{19,20}.

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3 Furthermore, primary tumors under AS did not significantly grow (i.e. ≥ 3 mm diameter
4 increase) in 93% to 95% of individuals over this time period^{19,20}. Moreover, all cases of
5 disease progression under AS were successfully cured with surgery^{19,20} and the
6 majority of patients who initially accepted AS, avoided thyroid surgery (84-94% over
7 about 5-6 years)^{19,20}. Furthermore, in a recently published report from an ongoing
8 American AS study, Tuttle et al. reported low rates of tumor growth (3.8% of cases) and
9 no evidence of incident metastatic disease, in a cohort of 291 PTC patients whose
10 primary tumor was ≤ 1.5 cm in maximal diameter (median 25 month follow-up period)²¹.
11 A highly important consideration is the extent to which AS may be considered as an
12 acceptable disease management by patients diagnosed with low risk PTC. In the largest
13 study of AS in Japan, 55% of individuals with papillary microcarcinoma chose to
14 undergo AS, when offered this option or surgery.²² Similar data are not yet available
15 from other parts of the world. However, the recent report of 291 patients with low risk
16 PTC have been enrolled in an AS study in the United States,²¹ suggests that there may
17 be interest in this option in North America. In an in-depth qualitative study from the
18 same institution, the rationale for patient choice of surgery or AS was studied 15
19 patients.²³ In this study, D'Agostino et al. reported that that patients who opted for
20 surgery perceived a strong threat of the disease and were motivated to cure the
21 malignancy, whereas those who chose AS perceived the disease to be relatively
22 indolent and were motivated to avoid living without their thyroid (and possible reliance
23 on thyroid hormone replacement)²³. The frequency with which Canadian with low risk
24 PTC would prefer AS or surgery (and the rationale for the choice), is unknown.
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26 Furthermore, prospectively collected quantitative data on decision-making process and
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3 relevant psychosocial/quality of life patient reported outcomes are needed for low risk
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5 PTC patients offered the options of surgery or AS.
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8 **DESIGN, METHODS AND ANALYSIS**

9 **Study design and setting**

10
11 We are conducting a multi-phase prospective observational study of patients with low
12
13 risk PTC. The study is currently being conducted at the University Health Network
14
15 (UHN) hospitals in Toronto (including Toronto General Hospital, Princess Margaret
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17 Cancer Centre, and Toronto Western Hospital), with the plan to add additional sites, if
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19 feasible.
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24 **Study aim and primary outcomes in respective study phases**

25
26 In the first phase of this study, our aim is to prospectively examine the decision-making
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28 process of patients with low risk PTC considering surgery or active surveillance and the
29
30 primary outcome is the frequency (percentage) of patients choosing AS or surgery,
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32 respectively. In the second phase of the study, consenting patients who completed the
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34 first phase of the study are followed in the respective study arms of a) active
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36 surveillance, or b) surgery (according to patient choice). The primary outcome in the
37
38 second phase of the study is decision regret (with respect to the decision on AS or
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40 surgery, to be described in respective arms).
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46 **The study population eligibility criteria and recruitment**

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48 In the first phase of the study, we are enrolling consenting eligible adults (age ≥ 18
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50 years) with surgically untreated low risk PTC that is confined to the thyroid, not
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52 immediately adjacent to critical structures in the neck (e.g. trachea or recurrent
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54 laryngeal nerve), and measures < 2 cm in maximal diameter (Table 1). The inclusion
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3 criteria, relating to the primary tumor characteristics, were reviewed and approved (by
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5 consensus) by all thyroid cancer surgeons in our institution. In the first study phase,
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7 study participants are provided verbal and written information about thyroid cancer
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9 disease prognosis and information about AS. This information is regularly updated to
10
11 reflect the evolving evidence on long-term outcomes with AS of low risk PTC.
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14 Participants are free to choose either surgery or AS for management of their thyroid
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16 cancer. Eligible consenting patients who have completed the first phase of this study
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18 (and rendered a disease management decision) may enroll in the second phase of the
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20 study, which includes study follow-up of respective disease management arms of: a)
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22 active surveillance, or b) thyroid cancer surgery. Patient recruitment is focused in
23
24 participating thyroid cancer surgical clinics, although eligible patients may be referred by
25
26 other healthcare providers or self-referred. All patients receive a formal consultation
27
28 from a thyroid cancer surgeon (of their choice) prior to consideration of enrollment in
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30 any phase of the study. Patients who may be eligible for the study, are offered the
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32 opportunity to meet with a research assistant. Screening for eligibility is performed by a
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34 research assistant, under the supervision of one or more of the primary co-primary
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36 investigators (DPG, AMS). Baseline neck imaging studies are reviewed by a study
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38 radiologist (SG) and surgeon (DPG) to confirm eligibility.
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46 **Study follow-up assessments and outcomes**

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49 In the first phase of the study (decision-making phase), a baseline medical history,
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51 physical examination and laryngoscopy (if not already performed), are performed.
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54 Several questionnaires are administered at baseline (prior to the presentation of the
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56 information about AS), as well as after the disease management decision on AS or
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3 surgery is finalized (generally within a few months of study enrollment). Baseline
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5 questionnaires include questions on demographic and medical history, coping
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7 mechanisms (Brief Cope Questionnaire²⁴), fear of disease progression (Short form of
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9 the Fear of Progression Questionnaire^{25,26}), fear of surgery (Surgical Fear
10
11 Questionnaire²⁷), and decision self-efficacy (Decision Self-Efficacy Scale²⁸). The primary
12
13 outcome is the frequency with which either disease management option is chosen by
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15 the patient (AS or immediate surgery). Secondary outcomes include: rationale for the
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17 decision, role of the patient in decision-making, and decision satisfaction²⁹.
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22 In the second phase of the study, consenting eligible adult patients who completed the
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24 first study phase may enroll in a follow-up study of respective AS or surgery arms. The
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26 active surveillance arm includes follow-up assessments by study investigators at least
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28 every 6 months for two years, followed by yearly (if no evidence of disease
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30 progression). These assessments include clinical history and examination, neck
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32 ultrasound, and measurement of TSH, free thyroxine, thyroglobulin, and thyroglobulin
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34 antibody. More frequent assessments or additional investigations may be arranged,
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36 depending on clinical circumstances. Thyroid hormone treatment is offered as per
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38 current clinical practice guidelines for chronic management of low risk PTC¹³, but its use
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40 is not mandated for participation in the AS follow-up study. The criteria for disease
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42 progression prompting a recommendation for surgery are shown in Table 2. All patients
43
44 under active surveillance are free to choose to have surgery at any time point, in
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46 absence of disease progression. For consenting patients who choose surgery for
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48 primary management of their disease, the treating surgeon and patient will decide on
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50 the extent of the surgery and associated clinical follow-up. For study participants in
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3 either arm that undergo thyroid cancer surgery, there are no restrictions on which
4 surgeon or where the surgery may be performed (i.e. as per patient choice).
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9 One year after enrollment in the respective AS or surgical follow-up study arms, the
10 following study outcomes are examined: decision regret about disease management
11 choice (primary outcome) (Decision Regret Scale³⁰), psychological distress (depression
12 and anxiety, measured by the Hospital Depression and Anxiety Scale³¹), disease-
13 specific quality of life (measured by the thyroid cancer module of the MD Anderson
14 Symptom Inventory³²), fear of disease progression^{25,26}, and body image satisfaction
15 (measured by the Body Image Scale³³). Furthermore, thyroid cancer-related medical
16 records are examined in all patients to evaluate for disease progression, cross-over to
17 surgery in the AS group, new chronic thyroid hormone use, and thyroid cancer-related
18 healthcare resource utilization. Consent for review of medical records is requested for a
19 minimum of 3 years, but an optional consent is requested for review of records up to 10
20 years. However, indefinite clinical follow-up is offered for patients under AS, who do not
21 undergo surgery.
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39 40 **Statistical considerations**

41 42 **Sample size calculation**

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44 There is no a priori calculated sample size for the first phase of the study (on medical
45 decision-making), as it is a descriptive study incorporating a convenience sample;
46 however, the study will continue enrolling patients to adequately power meaningful
47 analysis of the primary outcome in the follow-up study. As our primary analysis for the
48 second phase of the study is a description of the level of decision regret in the
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respective AS and surgical arms at 1 year, a convenience sample should technically suffice. However, we are planning a secondary analysis, comparing decision regret between the AS and surgical groups, assuming sufficient sample size, so a sample size justification for that analysis is herein provided. There is no published data on what difference in level of regret is considered unimportant, so we chose our non-inferiority boundary based on the following considerations. Pilot decision regret data collected on a low risk PTC sample of 74 patients in a treatment decision making showed a between-patient standard deviation of 16 points (Sawka unpublished). Norman reported that across a wide range of questionnaires, the minimally important difference (MID) was around one half a standard deviation³⁴. The non-inferiority boundary should be smaller than the MID, as it represents an unimportant difference. We select a value of 0.375 SD or 6 points. The decision regret scale sums scores on 5 questions, each scored 1-5 and transforms to a 0-100 range³⁰. This means that a difference of one level on one question corresponds to 5 points on the final scale. Our non-inferiority boundary allows an average difference of 1 level on one question, but little more. The level of decision regret in the AS group will be considered non-inferior if the upper end of the 95% one-sided interval for the difference in mean regret scores lies below the value of the non-inferiority boundary. The minimum sample size required to demonstrate that decision regret is not inferior at 1 year in patients choosing AS compared to those choosing thyroid surgery, is a total of 180 patients from the combined study arms (assuming 80% power, a one-sided 95% confidence interval, and a MID of 6 points on the decision regret questionnaire). As there may be some attrition during the study, we will target a combined sample size from the follow-up arms of approximately 200

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3 patients. We cannot control the number of patients enrolling in either arm, as the
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5
6 ultimate treatment decision is based on patient choice.
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8 **Statistical analysis**

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10 The first phase of the study (AS or surgery decision-making) is a descriptive study, and
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12 the primary outcome of percentage (and 95% confidence intervals) of study participants
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14 who ultimately choose AS or surgery. Demographic and disease characteristics will be
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16 descriptively summarized, with means and standard deviations for continuous outcome
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18 and number and percentages for categorical outcomes. All baseline questionnaire data
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20 will be scored as per developers, for total scores or subscale scores and results
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22 summarized for the entire study population (as well as the ultimate disease
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24 management subgroups). If there is a sufficient number of patients in both AS and
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26 surgical groups, then we will compare the baseline characteristics between groups,
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28 using unpaired Student's t-tests. Furthermore, if there is a sufficient number of patients
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30 for analysis, a predictive analysis examining predictors of choosing AS, will be
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32 performed using a logistic regression analysis (incorporating demographic and disease
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34 factors). We will use a previously reported concurrent mixed methods approach^{35,36} to
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36 ascertain patients' reasons for treatment choice, by collecting data from semi-structured
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38 questions, coding responses, and identifying themes.
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46 In the follow-up phase of the study, the primary analysis will be a descriptive analysis of
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48 the level of decision regret³⁰, expressed as a mean and standard deviation in the AS
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50 arm and surgical arm, respectively. Assuming a sufficient number of participants in both
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52 the AS and surgical arm for meaningful analysis, an unpaired Student's t-test will be
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54 performed, comparing decision regret scores in each group. The comparative analysis
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3 of decision regret scores between groups will be a non-inferiority (one-sided)
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5 comparison. Other quantitative data from all other questionnaires for each treatment
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7 subgroup will be summarized descriptively, as means and 95% confidence intervals, as
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9 appropriate for the questionnaire scores and subscale scores.
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12 **ETHICS AND DISSEMINATION**

13 **Informed consent**

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17 Informed consent is obtained from study participants enrolling in the respective parts of
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19 the study, including, 1) decision-making on disease management (AS or surgery), and
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21 2) a) active surveillance follow-up arm, b) surgical arm. Patients are assured that their
22
23 participation is voluntary and they may withdraw from the study at any time.
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27 Furthermore, for patients withdrawing from the study, assistance with arrangement of
28
29 continuity of clinical follow-up care will be offered, if needed. Furthermore, patients
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31 opting for AS may change their minds and have thyroid surgery at any point in follow-up
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33 (regardless of whether the disease has progressed or not). Participants may choose to
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35 provide optional consent for additional follow-up up to 10 years for any aspect of the
36
37 study.
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40 **Study registration, ethics review and data protection**

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43 This study is registered at Clinicaltrials.gov: NCT03271892. Research ethics board
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45 approval for the study has been obtained at UHN, in Toronto, Canada. If additional
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47 study sites are added, additional research ethics board approval will be obtained at all
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49 participating sites and UHN.
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52 **Access to data and dissemination**

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3 Only the study co-primary investigators (AMS, DPG), research staff, and statistician will
4 have access to the raw data, which will be securely stored. All participants are assigned
5 a unique study identifier number. No identifying patient information will be shared.
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8 Aggregate study results will be presented at scientific conferences and the results of the
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10 study published in one or more peer-reviewed open access journals. Study results will
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12 also be disseminated to local thyroid cancer specialists and patient support group
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14 representatives.
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19 **Recruitment and status of the study**

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21 This study is currently approved by the UHN Research Ethics Board and enrollment is
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23 in progress. The total duration of the study is expected to be up to 10 years and further
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25 research funding will be sought for support of long-term follow-up and outcome
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27 assessment.
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31 **Perspective**

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33 Management of low risk PTC is currently evolving, with a trend for providing more
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35 conservative options for patients who are at lowest risk of dying of their disease¹³.
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37 Active surveillance as been proposed as a means to mitigate potential overtreatment
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39 and treatment-related complications in patients with low risk PTC¹⁶⁻¹⁸. Furthermore, in
40
41 Japan, AS has emerged as a viable treatment option for papillary microcarcinoma^{19,20}.
42
43 Yet outside of Japan, the acceptability of AS among patients with low risk PTC is
44
45 unknown, and more research is needed examining the long-term outcomes (clinical and
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47 psychosocial) in patients with larger tumor sizes. This prospective study is intended to
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49 complement that of existing research in AS of PTC from other parts of the world, and
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3 inform potential expansion of disease management options for future patients with low
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5 risk PTC.
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10 **Contributors** The co-primary investigators, DPG and AMS designed the study,
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12 obtained funding for the study, oversee all aspects of execution and reporting of the
13
14 study. SG has provided input in study design, and is the primary study radiologist,
15
16 providing input on interpretation of ultrasound imaging of the neck. All of the surgeon
17
18 investigators have provided input in study design, are active in assisting in participant
19
20 recruitment for the study, and provided input on this manuscript (LR, RG, PG, JP, DB,
21
22 JDA, JI, DC, KD, KH, EM). GT, JJ, and AG have provided input in methodologic aspects
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24 of the study design and assisted in the application for study funding. GT is the
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statistician overseeing analysis of the study results. All authors have approved the final manuscript.

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Competing Interests None declared.

Ethics approval This study is approved by the University Health Network Research Ethics Board in Toronto, Canada.

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2
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5
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7
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10 Danzie.
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Table 1.

Details of Study Inclusion and Exclusion Criteria (At baseline assessment, prior to deciding on surgery or active surveillance)*	
<i>Inclusion criteria</i>	<i>Exclusion criteria</i>
Age ≥18 years	Known regional or distant metastatic thyroid cancer at the time of baseline evaluation (prior to thyroid cancer surgery)
Newly diagnosed, previously untreated papillary thyroid cancer (PTC) < 2cm in maximal diameter on ultrasound imaging. Fine needle aspiration biopsy of the primary tumor must be read as either PTC or suspicious for PTC (as reviewed by a cytopathologist at a participating study site).	A history of prior thyroid cancer surgery
No evidence of metastatic cervical lymphadenopathy on ultrasound imaging of the neck (or other neck imaging).	The primary PTC is adjacent to the recurrent laryngeal nerve or trachea
No other potential indication for thyroid or parathyroid surgery at the time of the assessment.	Known or suspected poorly differentiated or non-papillary thyroid cancer
Patient permission must be granted for review of thyroid cancer-related medical	Medically unfit for surgery due to co-morbidity

records to determine study eligibility	
	Another active malignancy (excluding non-melanoma skin cancer) for which patients are receiving treatment or are less than 3 years from completing treatment.
	Pregnancy at the time of study enrollment
	Other current indications for thyroid or parathyroid surgery
	Patient is unable to provide informed consent for the study or comply with study follow-up procedures due to current severe active cognitive or psychiatric impairment, substance abuse, or other reasons.

*Eligible consenting patients participating in the respective follow-up arms of the study (ie. active surveillance or surgery), must have been enrolled the first phase of the study, where standardized information about PTC prognosis and active surveillance is offered. Consenting eligible patients in the surgical follow-up arm are enrolled after first thyroid cancer surgery is completed.

Table 2.

Definition of progression of papillary thyroid cancer under active surveillance for which salvage surgery is advised (one or more of the criteria listed below)*
1. Primary index PTC growth >3 mm, confirmed on two consecutive ultrasound exams. The 3 mm size cut off has been shown to be safe and effectively treated in prior VL-PTC AS studies (19,20,22) and is considered reproducible (37).
2. Primary PTC growth in a location that is concerning (e.g. immediately adjacent to the trachea or in the course of the recurrent laryngeal nerve).
3. Incident development of metastatic PTC to lymph nodes (confirmed on cytology or unequivocal imaging)
4. Incident development of distant metastatic PTC (confirmed on imaging or biopsy or surgical histology)

*Patients may choose to have surgery in absence of disease progression at any time point in follow-up

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A Protocol for a Canadian Prospective Observational Study of Decision-making on Active Surveillance or Surgery for Low Risk Papillary Thyroid Cancer

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Manuscripts

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3 **A Protocol for a Canadian Prospective Observational Study of**
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5 **Decision-making on Active Surveillance or Surgery for**
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7 **Low Risk Papillary Thyroid Cancer**
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ABSTRACT

Introduction Low risk papillary thyroid cancer (PTC) is increasingly being diagnosed throughout the world; yet the mortality risk is low compared to other malignancies.

Traditional management includes thyroid surgery, sometimes followed by radioactive iodine and thyroid hormone treatment. Active surveillance (AS) has been proposed as a means to reduce over treatment of PTC. AS involves close disease follow-up, with the intention to intervene if the disease progresses, or upon patient request.

Methods and analysis This is a multi-phase prospective observational study. In the first phase of this study, consenting eligible adults with low risk PTC that is < 2cm in maximal diameter, confined to the thyroid, and not immediately adjacent to critical structures in the neck, are provided verbal and written information about PTC disease prognosis following surgery or AS. Questionnaires are administered at baseline and after the disease management decision on AS or surgery is finalized. Patients may choose either option (surgery or AS), and the primary outcome is the frequency with which either disease management option is chosen. Secondary outcomes include: rationale for the decision, role of the patient in decision-making, and decision satisfaction.

In the second phase of the study, consenting eligible adult patients who completed the first study phase may enroll in respective AS or surgery group follow-up studies. The following outcomes are examined 1 year after enrollment in the follow-up phase: decision regret about disease management choice (primary outcome), psychological distress, disease-specific quality of life, fear of disease progression, body image

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3 satisfaction, disease progression, cross-over to surgery in the AS group, new chronic
4 thyroid hormone use, and healthcare resource utilization.
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8 **Ethics and dissemination** The University Health Network Research Ethics Board
9 approved this study (ID 15-8942). The results will be published in an open access
10 journal.
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16 **Registration details** Clinicaltrials.gov: NCT03271892

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18 (<https://clinicaltrials.gov/ct2/show/NCT03271892?term=NCT03271892&cond=Thyroid+Cancer%2C+Papillary&cntry1=NA%3ACA&rank=1>)
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24 25 26 27 **Strengths and limitations of this study**

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30 • A strength of this study is that it is the first study to conduct a detailed
31 prospective evaluation of decision-making related to the choice of active
32 surveillance (AS) or immediate thyroid surgery, for management of low risk
33 papillary thyroid cancer (PTC).
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37 • Another strength of this study is the inclusion of secondary outcomes such as:
38 psychological distress (depression and anxiety), disease-specific quality of life,
39 fear of disease progression, and body image satisfaction, is an important
40 strength.
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44 • A limitation of this study is that participants are not randomized to AS or surgical
45 arms, as the choice of disease management is per the patient and treating
46 physician.
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- Another limitation of this study is that for patients who undergo thyroid cancer surgery, the surgical procedure and associated follow-up procedures are at the discretion of the treating physician and patient; which is intended to be reflective of usual care.

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INTRODUCTION

Increased utilization of diagnostic imaging has resulted in increased diagnosis of incidental malignancies that have a low risk of progression or death.¹ Some recent annual estimates on the number of individuals newly diagnosed with thyroid cancer include: 298,000 world-wide², 7,100 in Canada³, 56,870 in the United States⁴, 53,000 in Europe⁵, and 3,400 in the United Kingdom². In Canada, TC incidence is rising faster than any other malignancy³, with an increase of 156% from 1991 to 2006⁶. The survival rate of thyroid cancer is among the highest of all malignancies^{3,4} and the 5-year survival rate for early stage (local) thyroid cancer is reported to be >99%⁴. Most of the increase in thyroid cancer incidence is attributed to detection of papillary thyroid cancer (PTC) \leq 2cm in diameter⁷⁻¹¹, especially, localized disease without metastases (i.e. no spread of disease beyond the thyroid)^{8,11,12}. PTCs \leq 2 cm in diameter are estimated to account for 60-68% of new cases^{7,9}. Thyroid cancer treatment traditionally involves thyroid surgery, which may be followed by thyroid hormone replacement (lifelong) and radioactive iodine treatment¹³⁻¹⁵. However, treatment-related morbidity in individuals at low risk of dying from their disease is a relevant concern; thus the consideration of an option for a conservative, non-operative management approach for select to low risk PTC cases, has been proposed by some experts¹⁶⁻¹⁸.

Active surveillance (AS) of a malignancy consists of close clinical/diagnostic test follow-up (in lieu of immediate surgery), with the intention of treatment with curative intent if the disease progresses or the patient requests it. In two recent prospective observational studies from Japan, patients with PTC \leq 1cm in diameter underwent AS and there were no TC-related deaths, no distant metastatic recurrences, and the rate of cervical lymph

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3 node recurrence was approximately 1 to 2% (followed on average for 5-6 years)^{19,20}.
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5 Furthermore, primary tumors under AS did not significantly grow (i.e. ≥ 3 mm diameter
6 increase) in 93% to 95% of individuals over this time period^{19,20}. Moreover, all cases of
7 disease progression under AS were successfully cured with surgery^{19,20} and the
8 majority of patients who initially accepted AS, avoided thyroid surgery (84-94% over
9 about 5-6 years)^{19,20}. Furthermore, in a recently published report from an ongoing
10 American AS study, Tuttle et al. reported low rates of tumor growth (3.8% of cases) and
11 no evidence of incident metastatic disease, in a cohort of 291 PTC patients whose
12 primary tumor was ≤ 1.5 cm in maximal diameter (median 25 month follow-up period)²¹.
13
14 A highly important consideration is the extent to which AS may be considered as an
15 acceptable disease management by patients diagnosed with low risk PTC. In the largest
16 study of AS in Japan, 55% of individuals with papillary microcarcinoma chose to
17 undergo AS, when offered this option or surgery.²² Similar data are not yet available
18 from other parts of the world. However, the recent report of 291 patients with low risk
19 PTC have been enrolled in an AS study in the United States,²¹ suggests that there may
20 be interest in this option in North America. In an in-depth qualitative study from the
21 same institution, the rationale for patient choice of surgery or AS was studied 15
22 patients.²³ In this study, D'Agostino et al. reported that that patients who opted for
23 surgery perceived a strong threat of the disease and were motivated to cure the
24 malignancy, whereas those who chose AS perceived the disease to be relatively
25 indolent and were motivated to avoid living without their thyroid (and possible reliance
26 on thyroid hormone replacement)²³. The frequency with which Canadian with low risk
27 PTC would prefer AS or surgery (and the rationale for the choice), is unknown.
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3 Furthermore, prospectively collected quantitative data on decision-making process and
4 relevant psychosocial/quality of life patient reported outcomes are needed for low risk
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8 PTC patients offered the options of surgery or AS.
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10 **DESIGN, METHODS AND ANALYSIS**

11 **Study design and setting**

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14 We are conducting a multi-phase prospective observational study of patients with low
15 risk PTC. The study is currently being conducted at the University Health Network
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17 (UHN) hospitals in Toronto (including Toronto General Hospital, Princess Margaret
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19 Cancer Centre, and Toronto Western Hospital), with the plan to add additional sites, if
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22 feasible.
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26 **Study aim and primary outcomes in respective study phases**

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28 In the first phase of this study, our aim is to prospectively examine the decision-making
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30 process of patients with low risk PTC considering surgery or active surveillance and the
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32 primary outcome is the frequency (percentage) of patients choosing AS or surgery,
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34 respectively. In the second phase of the study, consenting patients who completed the
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36 first phase of the study are followed in the respective study arms of a) active
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38 surveillance, or b) surgery (according to patient choice). The primary outcome in the
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40 second phase of the study is decision regret (with respect to the decision on AS or
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42 surgery, to be described in respective arms).
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47 **The study population eligibility criteria and recruitment**

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49 In the first phase of the study, we are enrolling consenting eligible adults (age ≥ 18
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51 years) with surgically untreated low risk PTC that is confined to the thyroid, not
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53 immediately adjacent to critical structures in the neck (e.g. trachea or recurrent
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3 laryngeal nerve), and measures <2cm in maximal diameter (Table 1). The inclusion
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5 criteria, relating to the primary tumor characteristics, were reviewed and approved (by
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7 consensus) by all thyroid cancer surgeons in our institution. In the first study phase,
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9 study participants are provided verbal and written information about thyroid cancer
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11 disease prognosis and information about AS. This information is regularly updated to
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13 reflect the evolving evidence on long-term outcomes with AS of low risk PTC.
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16 Participants are free to choose either surgery or AS for management of their thyroid
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18 cancer. Eligible consenting patients who have completed the first phase of this study
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20 (and rendered a disease management decision) may enroll in the second phase of the
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22 study, which includes study follow-up of respective disease management arms of: a)
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24 active surveillance, or b) thyroid cancer surgery. Patient recruitment is focused in
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26 participating thyroid cancer surgical clinics, although eligible patients may be referred by
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28 other healthcare providers or self-referred. All patients receive a formal consultation
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30 from a thyroid cancer surgeon (of their choice) prior to consideration of enrollment in
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32 any phase of the study. Patients who may be eligible for the study, are offered the
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34 opportunity to meet with a research assistant. Screening for eligibility is performed by a
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36 research assistant, under the supervision of one or more of the primary co-primary
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38 investigators (DPG, AMS). Baseline neck imaging studies are reviewed by a study
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40 radiologist (SG) and surgeon (DPG) to confirm eligibility.
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48 **Study follow-up assessments and outcomes**

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51 In the first phase of the study (decision-making phase), a baseline medical history,
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53 physical examination and laryngoscopy (if not already performed), are performed.
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55 Several questionnaires are administered at baseline (prior to the presentation of the
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3 information about AS), as well as after the disease management decision on AS or
4 surgery is finalized (generally within a few months of study enrollment). Baseline
5 questionnaires include questions on demographic and medical history, coping
6 mechanisms (Brief Cope Questionnaire²⁴), fear of disease progression (Short form of
7 the Fear of Progression Questionnaire^{25,26}), fear of surgery (Surgical Fear
8 Questionnaire²⁷), and decision self-efficacy (Decision Self-Efficacy Scale²⁸). The primary
9 outcome is the frequency with which either disease management option is chosen by
10 the patient (AS or immediate surgery). Secondary outcomes include: rationale for the
11 decision, role of the patient in decision-making, and decision satisfaction²⁹.
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24 In the second phase of the study, consenting eligible adult patients who completed the
25 first study phase may enroll in a follow-up study of respective AS or surgery arms. The
26 active surveillance arm includes follow-up assessments by study investigators at least
27 every 6 months for two years, followed by yearly (if no evidence of disease
28 progression). These assessments include clinical history and examination, neck
29 ultrasound, and measurement of TSH, free thyroxine, thyroglobulin, and thyroglobulin
30 antibody. More frequent assessments or additional investigations may be arranged,
31 depending on clinical circumstances. Thyroid hormone treatment is offered as per
32 current clinical practice guidelines for chronic management of low risk PTC¹³, but its use
33 is not mandated for participation in the AS follow-up study. The criteria for disease
34 progression prompting a recommendation for surgery are shown in Table 2. All patients
35 under active surveillance are free to choose to have surgery at any time point, in
36 absence of disease progression. For consenting patients who choose surgery for
37 primary management of their disease, the treating surgeon and patient will decide on
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3 the extent of the surgery and associated clinical follow-up. For study participants in
4 either arm that undergo thyroid cancer surgery, there are no restrictions on which
5 surgeon or where the surgery may be performed (i.e. as per patient choice).
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11 One year after enrollment in the respective AS or surgical follow-up study arms, the
12 following study outcomes are examined: decision regret about disease management
13 choice (primary outcome) (Decision Regret Scale³⁰), psychological distress (depression
14 and anxiety, measured by the Hospital Depression and Anxiety Scale³¹), disease-
15 specific quality of life (measured by the thyroid cancer module of the MD Anderson
16 Symptom Inventory³²), fear of disease progression^{25,26}, and body image satisfaction
17 (measured by the Body Image Scale³³). Furthermore, thyroid cancer-related medical
18 records are examined in all patients to evaluate for disease progression, cross-over to
19 surgery in the AS group, new chronic thyroid hormone use, and thyroid cancer-related
20 healthcare resource utilization. Consent for review of medical records is requested for a
21 minimum of 3 years, but an optional consent is requested for review of records up to 10
22 years. However, indefinite clinical follow-up is offered for patients under AS, who do not
23 undergo surgery.
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41 **Statistical considerations**

42 **Sample size calculation**

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45 There is no a priori calculated sample size for the first phase of the study (on medical
46 decision-making), as it is a descriptive study incorporating a convenience sample;
47 however, the study will continue enrolling patients to adequately power meaningful
48 analysis of the primary outcome in the follow-up study. As our primary analysis for the
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3 second phase of the study is a description of the level of decision regret in the
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5 respective AS and surgical arms at 1 year, a convenience sample should technically
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7 suffice. However, we are planning a secondary analysis, comparing decision regret
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9 between the AS and surgical groups, assuming sufficient sample size, so a sample size
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11 justification for that analysis is herein provided. There is no published data on what
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13 difference in level of regret is considered unimportant, so we chose our non-inferiority
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15 boundary based on the following considerations. Pilot decision regret data collected on
16
17 a low risk PTC sample of 74 patients in a treatment decision making showed a
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19 between-patient standard deviation of 16 points (Sawka unpublished). Norman
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21 reported that across a wide range of questionnaires, the minimally important difference
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23 (MID) was around one half a standard deviation³⁴. The non-inferiority boundary should
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25 be smaller than the MID, as it represents an unimportant difference. We select a value
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27 of 0.375 SD or 6 points. The decision regret scale sums scores on 5 questions, each
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29 scored 1-5 and transforms to a 0-100 range³⁰. This means that a difference of one level
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31 on one question corresponds to 5 points on the final scale. Our non-inferiority boundary
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33 allows an average difference of 1 level on one question, but little more. The level of
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35 decision regret in the AS group will be considered non-inferior if the upper end of the
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37 95% one-sided interval for the difference in mean regret scores lies below the value of
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39 the non-inferiority boundary. The minimum sample size required to demonstrate that
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41 decision regret is not inferior at 1 year in patients choosing AS compared to those
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43 choosing thyroid surgery, is a total of 180 patients from the combined study arms
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45 (assuming 80% power, a one-sided 95% confidence interval, and a MID of 6 points on
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47 the decision regret questionnaire). As there may be some attrition during the study, we
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3 will target a combined sample size from the follow-up arms of approximately 200
4 patients. The enrollment in the first phase of the study (on the choice of AS or surgery)
5 will stop once 200 patients have been recruited in the combined AS and surgical arms
6 of the follow-up study. We cannot control the number of patients enrolling in either arm,
7 as the ultimate treatment decision is based on patient choice; thus our recruitment
8 target is based on the total number of patients in both follow-up study arms.
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16 **Statistical analysis**

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19 The first phase of the study (AS or surgery decision-making) is a descriptive study, and
20 the primary outcome of percentage (and 95% confidence intervals) of study participants
21 who ultimately choose AS or surgery. Demographic and disease characteristics will be
22 descriptively summarized, with means and standard deviations for continuous outcome
23 and number and percentages for categorical outcomes. All baseline questionnaire data
24 will be scored as per developers, for total scores or subscale scores and results
25 summarized for the entire study population (as well as the ultimate disease
26 management subgroups). If there is a sufficient number of patients in both AS and
27 surgical groups, then we will compare the baseline characteristics between groups,
28 using unpaired Student's t-tests. Furthermore, if there is a sufficient number of patients
29 for analysis, a predictive analysis examining predictors of choosing AS, will be
30 performed using a logistic regression analysis (incorporating demographic and disease
31 factors). We will use a previously reported concurrent mixed methods approach^{35,36} to
32 ascertain patients' reasons for treatment choice, by collecting data from semi-structured
33 questions, coding responses, and identifying themes.
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3 In the follow-up phase of the study, the primary analysis will be a descriptive analysis of
4 the level of decision regret³⁰, expressed as a mean and standard deviation in the AS
5 arm and surgical arm, respectively. Assuming a sufficient number of participants in both
6 the AS and surgical arm for meaningful analysis, an unpaired Student's t-test will be
7 performed, comparing decision regret scores in each group. The comparative analysis
8 of decision regret scores between groups will be a non-inferiority (one-sided)
9 comparison. Other quantitative data from all other questionnaires for each treatment
10 subgroup will be summarized descriptively, as means and 95% confidence intervals, as
11 appropriate for the questionnaire scores and subscale scores.
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23 **ETHICS AND DISSEMINATION**

24 **Informed consent**

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28 Informed consent is obtained from study participants enrolling in the respective parts of
29 the study, including, 1) decision-making on disease management (AS or surgery), and
30 2) a) active surveillance follow-up arm, b) surgical arm. Patients are assured that their
31 participation is voluntary and they may withdraw from the study at any time.
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37 Furthermore, for patients withdrawing from the study, assistance with arrangement of
38 continuity of clinical follow-up care will be offered, if needed. Furthermore, patients
39 opting for AS may change their minds and have thyroid surgery at any point in follow-up
40 (regardless of whether the disease has progressed or not). Participants may choose to
41 provide optional consent for additional follow-up up to 10 years for any aspect of the
42 study.
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51 **Study registration, ethics review and data protection**

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3 This study is registered at Clinicaltrials.gov: NCT03271892. Research ethics board
4 approval for the study has been obtained at UHN, in Toronto, Canada. If additional
5 study sites are added, additional research ethics board approval will be obtained at all
6 participating sites and UHN.
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10 11 12 **Access to data and dissemination**

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14 Only the study co-primary investigators (AMS, DPG), research staff, and statistician will
15 have access to the raw data, which will be securely stored. All participants are assigned
16 a unique study identifier number. No identifying patient information will be shared.
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18 Aggregate study results will be presented at scientific conferences and the results of the
19 study published in one or more peer-reviewed open access journals. Study results will
20 also be disseminated to local thyroid cancer specialists and patient support group
21 representatives.
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30 31 **Recruitment and status of the study**

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33 This study is currently approved by the UHN Research Ethics Board and enrollment is
34 in progress. The total duration of the study is expected to be up to 10 years and further
35 research funding will be sought for support of long-term follow-up and outcome
36 assessment. An important limitation of our study is that we do not have preliminary pilot
37 data on the feasibility of recruitment of Canadian low risk thyroid cancer patients in the
38 active surveillance arm. However, at the current recruitment rate, it appears that our
39 recruitment target will be achieved within the 10 year time frame of the study.
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49 **Perspective**

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51 Management of low risk PTC is currently evolving, with a trend for providing more
52 conservative options for patients who are at lowest risk of dying of their disease¹³.
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3 Active surveillance as been proposed as a means to mitigate potential overtreatment
4 and treatment-related complications in patients with low risk PTC¹⁶⁻¹⁸. Furthermore, in
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6 Japan, AS has emerged as a viable treatment option for papillary microcarcinoma^{19,20}.
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8 Yet outside of Japan, the acceptability of AS among patients with low risk PTC is
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10 unknown, and more research is needed examining the long-term outcomes (clinical and
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12 psychosocial) in patients with larger tumor sizes. This prospective study is intended to
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14 complement that of existing research in AS of PTC from other parts of the world, and
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16 inform potential expansion of disease management options for future patients with low
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18 risk PTC. It is important to note that long-term follow-up of patients enrolled in this, and
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20 other studies, examining active surveillance of low risk PTC is needed.
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28 **Contributors** The co-primary investigators, DPG and AMS designed the study,
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30 obtained funding for the study, oversee all aspects of execution and reporting of the
31
32 study. SG has provided input in study design, and is the primary study radiologist,
33
34 providing input on interpretation of ultrasound imaging of the neck. All of the surgeon
35
36 investigators have provided input in study design, are active in assisting in participant
37
38 recruitment for the study, and provided input on this manuscript (LR, RG, PG, JP, DB,
39
40 JDA, JI, DC, KH, EM). GT, JJ, and AG have provided input in methodologic aspects of
41
42 the study design and assisted in the application for study funding. GT is the statistician
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44 overseeing analysis of the study results. All authors have approved the final
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46 manuscript.
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53 obtained from an operating grant (Innovation Grant) from the Ontario Academic Health
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4
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6
7 an operating grant from the Canadian Cancer Society Research Institute (The Lotte and
8
9 John Hecht Memorial Foundation Innovation Grant, #703948).

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12 **Competing Interests** None declared.

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15 **Ethics approval** This study is approved by the University Health Network Research
16
17 Ethics Board in Toronto, Canada.

18
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27 Danzie.
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view only

Table 1.

Details of Study Inclusion and Exclusion Criteria (At baseline assessment, prior to deciding on surgery or active surveillance)*	
<i>Inclusion criteria</i>	<i>Exclusion criteria</i>
Age ≥18 years	Known regional or distant metastatic thyroid cancer at the time of baseline evaluation (prior to thyroid cancer surgery)
Newly diagnosed, previously untreated papillary thyroid cancer (PTC) < 2cm in maximal diameter on ultrasound imaging. Fine needle aspiration biopsy of the primary tumor must be read as either PTC or suspicious for PTC (as reviewed by a cytopathologist at a participating study site).	A history of prior thyroid cancer surgery
No evidence of metastatic cervical lymphadenopathy on ultrasound imaging of the neck (or other neck imaging).	The primary PTC is adjacent to the recurrent laryngeal nerve or trachea
No other potential indication for thyroid or parathyroid surgery at the time of the assessment.	Known or suspected poorly differentiated or non-papillary thyroid cancer
Patient permission must be granted for review of thyroid cancer-related medical	Medically unfit for surgery due to co-morbidity

records to determine study eligibility	
	Another active malignancy (excluding non-melanoma skin cancer) for which patients are receiving treatment or are less than 3 years from completing treatment.
	Pregnancy at the time of study enrollment
	Other current indications for thyroid or parathyroid surgery
	Patient is unable to provide informed consent for the study or comply with study follow-up procedures due to current severe active cognitive or psychiatric impairment, substance abuse, or other reasons.

*Eligible consenting patients participating in the respective follow-up arms of the study (ie. active surveillance or surgery), must have been enrolled the first phase of the study, where standardized information about PTC prognosis and active surveillance is offered. Consenting eligible patients in the surgical follow-up arm are enrolled after first thyroid cancer surgery is completed.

Table 2.

Definition of progression of papillary thyroid cancer under active surveillance for which salvage surgery is advised (one or more of the criteria listed below)*
1. Primary index PTC growth >3 mm, confirmed on two consecutive ultrasound exams. The 3 mm size cut off has been shown to be safe and effectively treated in prior VL-PTC AS studies (19,20,22).
2. Primary PTC growth in a location that is concerning (e.g. immediately adjacent to the trachea or in the course of the recurrent laryngeal nerve).
3. Incident development of metastatic PTC to lymph nodes (confirmed on cytology or unequivocal imaging)
4. Incident development of distant metastatic PTC (confirmed on imaging or biopsy or surgical histology)

*Patients may choose to have surgery in absence of disease progression at any time point in follow-up

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