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Anna (Annie) Sawka, MD, PhD, FRCPC
Professor, Dept. of Medicine, University of Toronto
Affiliate Scientist, Toronto General Hospital Research Institute
200 Elizabeth Street, 12 EN-212, Toronto, Ontario M5G 2C4

The Canadian Society of Endocrinology and Metabolism (CSEM) and the Thyroid Foundation of Canada: Application for the Thyroid Foundation of Canada Research Award

To the CSEM Awards Committee,

We respectfully submit a grant proposal for a study titled, "*Physicians' Opinions on Active Surveillance and Minimally Invasive Ablative Treatment of Small, Low Risk Papillary Thyroid Cancer: A Global Cross-sectional Survey*" for consideration of funding from the Thyroid Foundation of Canada Research Award.

I am a Professor in the Department of Medicine (Endocrinology) and an Affiliate Scientist at the Toronto General Hospital Research Institute. I am an active CSEM member (ID 10224333). I am the principal applicant and I am the current Editor-in-Chief, of the journal, *Thyroid*, which is the flagship journal of the American Thyroid Association. I am also the primary investigator on an ongoing pan-Canadian study offering patients the choice of active surveillance or surgery for primary management of small, low risk PTC. I have experience in knowledge translation, medical guideline development, and administration of physician surveys. The co-investigator on this application is Dr. Heather Lochnan, an expert in thyroid cancer, is a Professor of Medicine at the University of Ottawa and past president of the CSEM. Dr. Lochnan and I have access to a wide network of thyroid cancer specialist physicians and surgeons across Canada and the world to build a collaborative research team and enable physician participation in our planned survey. Dr. Lochnan, as Assistant Dean of Continuing Professional Development brings, expertise in best practices for physician education and knowledge translation.

Our aim is to conduct an online physician survey and describe, according to global region, physicians' knowledge and attitudes with respect to management of small, low risk PTC. Opinions on novel approaches for primary management of small, low risk papillary thyroid cancer (PTC) include active surveillance (AS) or ultrasound guided minimally invasive ablative technologies (MIT) in lieu of traditional surgery will be the main focus. Active surveillance is an approach that involves close clinical follow-up and diagnostic testing (i.e. neck ultrasounds) according to a pre-established protocol and surgery is recommended if there is suspicion of tumor enlargement or other concerns about disease progression. It is fundamentally understood that patients who choose active surveillance can decide to have surgery at any time point, in the absence of progression, if they wish to do so. The role of minimally invasive ablative (ultrasound-guided) treatment (MIT) for primary management of PTC is currently in evolution. MIT uses ultrasound imaging to guide precise, localized treatment of a thyroid nodule/cancer or locally metastatic TC by means such as: ethanol injection, radiofrequency ablation, microwave, high-intensity focused ultrasound, or laser. AS and MIT are not universally available globally. Barriers and enablers to implementation of AS and MIT for management of small, low risk PTC will be examined in this study and this knowledge will be essential in informing planning of future health policies. We will use the knowledge gathered in this survey to develop an educational toolkit for Canadian physicians, regarding the options of AS and MIT for small, low risk PTC. The tool kit will include information about MIT (risks, benefits, appropriate use, and published clinical practice guideline recommendations), some tips on barriers and enablers to its implementation, and links to resources (such as links to guidelines, clinical contacts, etc).

This research will inform future clinical strategies for offering patients with small, low risk PTC, the options of less invasive disease management choices as alternatives to surgery. This research will also enable expert development of an educational toolkit for Canadian physicians, so that they may better educate their patients about potential less invasive options for management of small, low risk PTC. The tool kit will also appropriately direct specialist referrals, thereby facilitating clinical practice implementation.

Thank you for your consideration.

Anna Sawka, MD, PhD, FRCPC

Physicians' Opinions on Active Surveillance and Minimally Invasive Ablative Treatment of Small, Low Risk Papillary Thyroid Cancer: A Global Cross-sectional Survey

Lay summary

Goals: We will perform an electronic, on-line survey of thyroid cancer specialist physicians from across the world to gain an understanding of physicians' knowledge, understanding, attitudes, and beliefs about newer, less invasive, strategies for management of small, low risk papillary thyroid cancer (PTC). These novel strategies include active surveillance (AS, close observation rather than immediate surgery) or minimally invasive ablative treatments (MIT, in which the cancer is subject to local treatment without surgery) for small, low risk PTC. We will examine differences in physicians' opinions according to the region where they practice. We will also explore factors that may enable the use of the application of novel non-surgical approaches to management of small, low risk papillary thyroid cancer in clinical practice. Barriers to the use of such approaches will also be examined. Special attention will be paid to the knowledge and opinions of Canadian physicians. We will use the knowledge collected in the survey to develop a Canadian-physician targeted educational toolkit about AS and MIT for PTC.

Background: Small, low risk PTC is the most common type of thyroid cancer and most patients with this type of cancer are considered at low risk of dying of this disease (hence it is referred to as low risk PTC). Thyroid surgery (total or partial thyroidectomy) is the traditional standard treatment for small, low risk papillary thyroid cancer and it often cures the cancer. However, thyroid cancer surgery may be associated with treatment complications and some patients need to take thyroid hormone replacement treatment for the rest of their lives after surgery. Patients with small, low risk papillary thyroid cancer have expressed some strong interest in alternative non-surgical approaches to manage their disease in hopes of reducing the risk of treatment side effects, maintaining quality of life, and, if possible, avoiding becoming dependent on taking thyroid medicine. A potential option for management of small, low risk PTC is active surveillance (AS), which involves close medical monitoring, with the intention to avoid surgery, unless the cancer progresses (i.e. grows or spreads outside the thyroid) or if the patient changes his/her mind and wants surgery. Minimally invasive ablative treatments for thyroid cancer use ultrasound imaging to guide precise, localized treatment of a thyroid cancer by means such as: ethanol alcohol injection, radiofrequency ablation, microwave, high-intensity focused ultrasound, or laser, with the intention of destroying the tumor. Clinical research and experience with AS and MIT are variable throughout the world. In Canada, AS and MIT are available largely in a clinical research setting and so many physicians may not be aware of such management approaches and not offer them to their patients.

Methods: In this international online physician survey study, we will work with thyroid societies and the Canadian Society of Endocrinology and Metabolism, to contact physicians who participate in the care of patients with thyroid cancer. We will ask physicians about their general knowledge, attitudes and current experience with respect to AS and MIT in management of small, low risk PTC. We will explore differences in opinions according to regions. We will also learn about factors that may enable or be barriers to the use of AS and MIT in clinical care of low risk PTC patients, according to region. We will use the knowledge gained from the survey to develop an educational toolkit for Canadian physicians regarding the options of AS and MIT for management of small, low risk PTC.

Significance: This research will inform physician knowledge gaps about the use of AS and MIT for management of small, low risk PTC and inform the development of an educational toolkit for Canadian physicians, so that they will be able to better understand and explain such options to interested patients.

Physicians' Opinions on Active Surveillance and Minimally Invasive Ablative Treatment of Small, Low Risk Papillary Thyroid Cancer: A Global Cross-sectional Survey *(Sawka AM)*

Background and Purpose

Worldwide, it is estimated that approximately 449,000 women and 137,000 men are diagnosed with thyroid cancer each year (1). In Canada in 2023, it is estimated that 4,400 women and 1,900 men were diagnosed with thyroid cancer in 2023 (2). Yet the mortality rate of Canadian thyroid cancer patients is among the lowest of malignancies (3). Concerns have been raised about potential overdiagnosis and overtreatment of small, low risk papillary thyroid cancer (which is the most common histologic type) and de-escalation of treatment of low risk differentiated thyroid cancer has been recommended in the most recent American Thyroid Association (ATA) guidelines on this disease in 2015 (3). Traditional treatment of small (< 2 cm in maximal diameter), low risk papillary thyroid cancer (PTC) has generally included thyroidectomy (total or partial) with or without radioactive iodine remnant ablation treatment (3). Some potential consequences of thyroid surgical treatment of thyroid cancer include surgical complications such as post-operative hemorrhage, anesthetic complications, hypoparathyroidism, recurrent laryngeal nerve injury, and others. Furthermore, thyroid hormone replacement is always needed after total thyroidectomy and sometimes after hemithyroidectomy.

Given the excellent long-term prognosis of small, low risk PTC and consideration of potential harms related to surgery, alternative options on management of small, low risk PTC have received increasing attention in the medical literature. Such alternatives may include: a) active surveillance, or b) minimally invasive ablative treatments for small low-risk thyroid cancer that is confined to the thyroid.

Active surveillance (AS) of low risk papillary microcarcinoma (measuring ≤1 cm in maximal diameter) was first introduced as an alternative to traditional surgical treatment in Japan in the 1990s (4,5). If the current ATA guidelines are followed (3), biopsy of subcentimetre suspicious thyroid nodules is avoided, but not all physicians follow guidelines and microcarcinomas are still diagnosed.

Active surveillance is an approach that involves close clinical follow-up and diagnostic testing (i.e. neck ultrasounds) according to a pre-established protocol and surgery is recommended if there is suspicion of tumor enlargement or other concerns about disease progression. It is fundamentally understood that patients who choose active surveillance can decide to have surgery at any time point, in the absence of progression, if they wish to do so. In recent years, published research on the long-term clinical outcomes of AS for small, low-risk PTC, has grown internationally (6-17). We introduced active surveillance as a disease management option to surgery in a Canadian prospective cohort study initiated in 2016 at University Health Network (UHN) in Toronto (18) and a pan-Canadian study offering this option is currently ongoing (19). Our preliminary findings suggest that there is substantial patient interest in active surveillance, with about three-quarters of patients with low risk PTC < 2 cm in maximal diameter choosing this option (20). AS has been initially considered (3) and more recently recommended (21,22) as a disease management option for PTC microcarcinoma in practice guidelines.

The role of minimally invasive ablative (ultrasound-guided) treatment (MIT) for primary management of PTC is currently in evolution, with a growing evidence basis in the literature. MIT uses ultrasound imaging to guide precise, localized treatment of a thyroid nodule/cancer or locally metastatic TC by means such as: ethanol injection, radiofrequency ablation, microwave, high-intensity focused ultrasound, or laser. MIT is available in specialized centres in the United States, Europe, and Asia, and only recently initiated in select Canadian sites. An international expert consensus panel has recommended that "ultrasound-guided ablation procedures may be considered in patients with suitable primary papillary microcarcinoma who are unfit for surgery or decline surgery or active surveillance" (23). Globally, there is more experience in the use of MIT for management of benign thyroid nodules, however experience for primary management of PTC, is growing (24).

Canadian physicians who have limited knowledge about AS or MIT are unlikely to inform their patients about such options, or refer them to specialists with expertise in these techniques. It is not unusual for patients to learn about such options on the internet, and when they ask about their physicians about them, be faced with skepticism. This study will help address physician knowledge gaps.

Physicians' Opinions on Active Surveillance and Minimally Invasive Ablative Treatment of Small, Low Risk Papillary Thyroid Cancer: A Global Cross-sectional Survey *(Sawka AM)*

In order to effectively implement the use of novel approaches such as AS or MIT in primary management of small, low risk PTC, it is important to first understand the knowledge, attitudes, and current practice of physicians as well as perceived barriers to implementation. Such information can inform the development of an educational toolkit for physicians. In the only Canadian physician survey that was conducted before the publication of the last ATA guidelines, we determined that less than 2% of Canadian specialists would recommend AS for primary management of papillary microcarcinoma (25). Yet the evidence and clinical guidelines have changed since then. Published surveys on physician opinions on AS for papillary microcarcinoma have been conducted in the United States (26-30), Japan (31), and Korea (32,33), but little is known about Canadian physicians. Furthermore, there are currently no published physician surveys regarding the use of MIT in small, localized PTC. More information is needed to understand physician knowledge gaps, or physician hesitation to adopt AS and MIT. This information will inform the development of a Canadian physician-focused educational toolkit about AS and MIT, aimed as a form of targeted knowledge translation for Canadian physicians.

Purpose

I. Our primary general aim is to conduct an online international physician survey of specialists that are typically involved in the care of thyroid cancer patients (i.e. endocrinologists, surgeons, and others) to examine regional differences in knowledge, attitudes, and disease management options for the treatment of small, low-risk, papillary thyroid cancer, with a particular focus on opinions on AS and MIT.

II. We will use the knowledge gathered in this survey to inform the development of an educational toolkit for Canadian physicians, regarding the options of AS and MIT for small, low risk PTC.

Objectives

I. Our primary objective is to conduct an online survey and describe, according to global region, physicians' preferences with respect to management of small, low risk PTC. We will report on physician demographic and practice characteristics, and examine physicians' general knowledge, attitudes and current experience with respect to AS and MIT in the primary management of low risk PTC. Barriers and enablers to implementation of AS and MIT for management of small, low risk PTC will also be examined, with attention to regional differences. We will specifically report Canadian physician subgroup results.

II.Our secondary objective is to develop an educational toolkit about AS and MIT for small, low risk PTC for Canadian physicians. The tool kit will include information about the options of AS and MIT (risks, benefits, appropriate use, and published clinical practice guideline recommendations), some tips on barriers and enablers to its implementation, and links to resources (such as links to guidelines, clinical contacts with expertise in these procedures to facilitate referrals, etc). Future toolkits may be developed for other global regions, targeted to the local context, which in many cases is determined by healthcare funding models and local expertise.

Hypothesis

We expect there will be marked regional variability in acceptance, knowledge, and implementation of AS and MIT and that the highest knowledge and strongest support will be in Asian countries, where such procedures have historically been more firmly established. We anticipate that Canadian physicians may have limited awareness of AS and MIT, and the vast majority will site a lack experience and will report barriers that need to be addressed for successful implementation of such procedures in practice.

Research design

We plan an international cross-sectional online physician survey. The survey will be web-based and mobile-accessible, and made available in multiple languages. We will use the latest version of Qualtrics software for administration of the survey. The following specialist organizations will be approached to help distribute the survey electronically (via e-mail) to their members (list subject to change): Canadian

Society of Endocrinology and Metabolism, American Thyroid Association, European Thyroid Association, Latin American Thyroid Society, and the Asia and Oceania Thyroid Association. Potential respondents will be contacted according to the regulations and bylaws of the participating societies. The study will be submitted for ethics review by the University Health Network Research Ethics Board.

An expert collaborative panel will be convened to develop and pilot-test the survey prior to distribution, with revisions made (according to language) as needed. The key concepts will be identified, the wording reviewed, and a consensus will be planned for the final version. Before release, the survey will be provided for review by the executive or research committees of participating organizations.

The potential participants will receive an initial email, and two reminder email invitations. The survey is expected to take about 10 minutes to complete and participants will select the language of their choice. There will be no compensation of physician participants. All responses will be anonymized. The planned software, Qualtrics, has built-in capacity to screen for and eliminate duplicate submissions.

We will collect self-reported data on demographic (age range, gender, race [optional]) and practice characteristics (e.g. country, specialty, years in practice, practice setting, practice volume, experience level with AS and MIT, and health system characteristics [e.g. private or publicly funding and health system coverage for AS or MIT]). General questions on knowledge and attitudes about AS and MIT for management of small, low-risk PTC will be asked. Barriers and enablers to AS and MIT implementation for low risk PTC will be examined.

For the purpose of analysis, we will group respondents according to practice location, as per the United Nations country grouping, however, Canadian-specific data will be grouped separately (assuming sufficient sample size for meaningful analysis). We anticipate a total of about 400 – 500 respondents, in considering the membership sizes of participating organizations, targeting physicians whose practice includes thyroid cancer, and published experience with a similarly designed survey on thyroid nodule management (35). This convenience sample should suffice for meaningful interpretation and reasonable precision estimates for descriptive data. The statistical analyses will be conducted by an experienced statistician. Descriptive data will be summarized and stratified by different subgroups of physicians. Univariate and multivariable logistic regression analyses will be performed for exploratory predictive analyses on treatment preferences.

The physician panelists who developed the survey will discuss the results via a virtual meeting and feedback will be obtained. The panelists will discuss the regional differences, and how enablers of successful implementation in countries using MIT and AS may inform Canadian practice. The panelists will use a modified delphi approach, using Welphi software online to develop a consensus draft of an educational toolkit on AS and MIT for small, low risk PTC for Canadian physicians. A graphic designer will assist with the layout of the final toolkit. The final toolkit will be reviewed by the physician panel.

Expectations

We expect to receive about 400 to 500 survey responses and that there will be a sufficient number of different global regions, that we will be able to meaningfully examine regional variability of the results. A draft of a Canadian-physician targeted toolkit about AS and MIT will be developed.

Potential pitfalls and how these will be addressed

The main potential pitfall is a potentially low participant response rate. The distribution of the survey through respective societies and multiple reminders mitigates this risk. Dr. Sawka (principal applicant) is Editor-in-Chief of Thyroid, and has access to global thyroid society collaborators. Dr. Lochnan, co-investigator, is a past CSEM President and will enable CSEM member participation.

Knowledge translation plan

We plan to present the results of this research at the CSEM meeting in 2025. We will also share our findings with the leadership of all participating societies and publish the findings (with open access).