

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Development of a Bi-National Thyroid Cancer Clinical Quality Registry: A Protocol Paper
AUTHORS	Ioannou, Liane; Serpell, Jonathan; Dean, Joanne; Bendinelli, Cino; Gough, Jenny; Lisewski, Dean; Miller, Julie; Meyer-Rochow, Win; Sidhu, Stan; Topliss, Duncan; Walters, David; Zalcborg, John; Ahern, Susannah

VERSION 1 – REVIEW

REVIEWER	Glenn D. Braunstein, M.D. Professor of Medicine, Cedars-Sinai Medical Center Los Angeles, CA 92660, USA
REVIEW RETURNED	26-Apr-2018

GENERAL COMMENTS	<p>The authors describe the protocol for establishing a thyroid cancer database. What they describe is really a thyroid cancer surgical database that collects data up to 90 days. As such, it will serve more of a surgical quality assurance project than a project that will look at such things as long term outcome such as local or distant recurrence based upon initial patient and tumor characteristics and surgical procedure, mortality, appropriate use of post-thyroidectomy radioactive iodine or effect of the degree of thyroid hormone suppression. In this regard, the investigators should look at National Thyroid Cancer Treatment Cooperative Study (NTCTCS) which is a long term registry that collects surgical data as well as long-term patient data and has contributed greatly to our current management of thyroid cancer. To be an effective tool to investigate the total management of thyroid cancer, the investigators should include endocrinologists as well as thyroid surgeons and endeavor to collect long-term data. This protocol will not answer some of the Registry Aims that the authors indicate will be addressed as it does not follow patients long enough.</p> <p>Specific comments:</p> <p>Protocol</p> <ol style="list-style-type: none">1. Page 7, section 3.3, 3rd paragraph: thyrotoxic storm is not a complication of surgery for thyroid carcinoma.2. same, 4th paragraph: you should explain that much of the increase incidence of thyroid cancer is due to incidental detection because of increased use of imaging.3. Page 12: Why limit your database to age ≥ 18? Thyroid cancer can occur at all ages and enhancing the knowledge of the management of pediatric thyroid cancer would be very useful as there is less data on the management in this age group than in adults.4. Page 13: The study only includes patients operated upon. More and more patients with well-differentiated thyroid cancer diagnosed by fine needle aspiration are being offered the option of
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	<p>active surveillance or surgery. It would be a shame to miss collecting information on this group.</p> <p>5. Page 13: This is a voluntary program for the surgeons. I would like to see this be a mandatory program for the surgeons operating at the selected institutions in order to avoid biasing the results. For instance maybe only high volume surgeons will participate while low volume surgeons may not be interested, and this group is likely to have the highest complication rate. It is important to get a true picture of what is being done in regards to surgical patient care, and not just by those surgeons who self-select themselves to participate.</p> <p>6. Page 16: what is the justification for collecting data for only 90 days?</p> <p>7. Page 18: you should be able to cross reference the completeness of patient ascertainment through a national surgical or national payment database.</p>
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REVIEWER	Iain Nixon NHS Lothian Edinburgh UK
REVIEW RETURNED	15-May-2018

GENERAL COMMENTS	<p>This is an interesting description of the development of a bi national clinical quality registry for thyroid cancer in Australia and New Zealand. It is difficult to know how best to try and add to this manuscript. It is well written and structured and I have no concern about the presentation of the work performed by the authors which is considerable.</p> <p>A few questions then:</p> <p>Table 1 presents clinical quality indicators. CQ4 is total thyroidectomy. However, increasingly there is a recognition that a significant group of patients will be suitable for a less than total thyroidectomy. Will this be represented as a potential indicator of clinical quality?</p> <p>Table 2: In pre operative data items FNA is mentioned. Which system (Bethesda / THY) do the authors plan to use. Would they also consider using an ultrasound grading system?</p> <p>In procedure they mention lymphovascular invasion and extra thyroidal extension. I wonder what exactly the group plan to collect. For example ETE will have to include macro versus micro if the 8th AJCC system is to be used. Also, lymphovascular invasion is very subjective. The categories yes/no may not be enough. no/suspicious/minimal(≤ 4)/extensive (>4) may be useful going forward.</p> <p>For staging, if accurate path and surgical data is included, TN (not M) can be inferred.</p> <p>Are the group planning to associate dates with the dynamic risk stratification data including Tg?</p> <p>In my version of figure 1 the opt out final box overlaps the data collection box. This may be a glitch at my end but is worth checking</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer Reports

Reviewer 1

The authors describe the protocol for establishing a thyroid cancer database. What they describe is really a thyroid cancer surgical database that collects data up to 90 days. As such, it will serve more of a surgical quality assurance project than a project that will look at such things as long term outcome such as local or distant recurrence based upon initial patient and tumour characteristics and surgical procedure, mortality, appropriate use of post-thyroidectomy radioactive iodine or effect of the degree of thyroid hormone suppression. In this regard, the investigators should look at National Thyroid Cancer Treatment Cooperative Study (NTCTCS) which is a long term registry that collects surgical data as well as long-term patient data and has contributed greatly to our current management of thyroid cancer. To be an effective tool to investigate the total management of thyroid cancer, the investigators should include endocrinologists as well as thyroid surgeons and endeavour to collect long-term data. This protocol will not answer some of the Registry Aims that the authors indicate will be addressed as it does not follow patients long enough.

The registry is currently in a pilot phase to assess feasibility and clinician acceptability. The protocol reflects the long-term aims of an ongoing registry following conclusion of the pilot, which will include longer-term multidisciplinary follow-up.

1. Page 7, section 3.3, 3rd paragraph: Thyrotoxic storm is not a complication of surgery for thyroid carcinoma.

This has not been included as a complication following surgery for thyroid cancer in the manuscript. We will remove thyrotoxic storm from the list of complications in the protocol in our next ethics amendment.

2. Same, 4th paragraph: You should explain that much of the increase incidence of thyroid cancer is due to incidental detection because of increased use of imaging.

As above this comment is based on our protocol, in our next protocol amendment we will include the following sentence: 'Much of the increased incidence of thyroid cancer is due to incidental detection as a result of increased imaging'. We also added this into the manuscript, please see tracked changes on page 4.

3. Page 12: Why limit your database to age ≥ 18 ? Thyroid cancer can occur at all ages and enhancing the knowledge of the management of paediatric thyroid cancer would be very useful as there is less data on the management in this age group than in adults.

The registry is currently in a pilot phase and is only recruiting patients from adult centres. We are working on an ethics amendment at the moment to extend the minimum age of recruitment to 16 years of age, as some adult centres see patients in this intermediate age group (16-18 years). After piloting the registry we will be expanding the registry to ensure state-wide capture in each jurisdiction which also include recruiting patients from children's hospitals with paediatric thyroid cancer.

4. Page 13: The study only includes patients operated upon. More and more patients with well-differentiated thyroid cancer diagnosed by fine needle aspiration are being offered the option of active surveillance or surgery. It would be a shame to miss collecting information on this group.

We agree that this is a management trend that, although uncommon in Australia currently, will likely become more common over time. The addition of such patients to the database will be considered, at the conclusion of the pilot, when the follow-up of the surgical group is extended beyond the immediate post-operative period (90-days) to enable longer-term data collection.

5. Page 13: This is a voluntary program for the surgeons. I would like to see this be a mandatory program for the surgeons operating at the selected institutions in order to avoid biasing the results. For instance maybe only high volume surgeons will participate while low volume surgeons may not be interested, and this group is likely to have the highest complication rate. It is important to get a true picture of what is being done in regards to surgical patient care, and not just by those surgeons who self-select themselves to participate.

The registry is supported by the Australian and New Zealand Thyroid Surgeons (ANZES), with all members paying a levy to contribute to the funding of the registry. We have developed various incentives to encourage participation by all surgeons at a participating site, including: patient-level and aggregate data reports in real-time; recognition by the Royal Australian College of Surgeons (RACS) as a Continuing Medical Education (CME) audit activity enabling fellows who participate to claim one point per hour in Surgical Audit & Audits of Surgical Mortality; ANZTCR valued contributor logos added to surgeons bio-page on the ANZES website and provided to surgeons to use at their discretion on their websites, email signatures, letterhead etc.; and, annual certificates to participating surgeons to recognise their valued contribution to the registry.

While most patient registries in Australia are not mandated, they are strongly encouraged by the relevant surgical association which has led to participation rates of over 80% in other surgical registries e.g. Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR); Prostate Cancer Outcomes Registry – Victoria (PCOR-Vic); and the Victorian Cardiac Outcomes Registry (VCOR).

6. Page 16: What is the justification for collecting data for only 90 days?

Registry funding is limited to data collection for up to 90-days postoperative. The limited funding does not allow for the inclusion of endocrinologists and the last time point for routine follow-up of surgical patients by surgeons is 3-months post-surgery (90-days). As mentioned previously, the registry will seek to include endocrinologists at the conclusion of the pilot, dependent on funding, to enable longer-term data collection.

7. Page 18: You should be able to cross reference the completeness of patient ascertainment through a national surgical or national payment database.

During the pilot phase ANZTCR staff will check case ascertainment periodically via comparison with each participating site's Health Information Services surgical activity data. In the future, to ensure case ascertainment, the ANZTCR will receive regular data extracts from participating site Health Information Services (HIS) or the Victorian Cancer Registry (VCR), pending approval.

Reviewer 2

This is an interesting description of the development of a bi-national clinical quality registry for thyroid cancer in Australia and New Zealand. It is difficult to know how best to try and add to this manuscript. It is well written and structured and I have no concern about the presentation of the work performed by the authors which is considerable.

1. Table 1 presents clinical quality indicators. CQI4 is total thyroidectomy. However, increasingly there is a recognition that a significant group of patients will be suitable for a less than total thyroidectomy. Will this be represented as a potential indicator of clinical quality?

The wording of the indicator in question is as follows: 'Patients with differentiated thyroid cancer who have advanced disease (extrathyroidal extension and/or metastatic disease) or tumour size >4 cm should undergo a total (or near-total) thyroidectomy'. A separate manuscript will be published on the development of the consensus set of clinical quality indicators for thyroid cancer. The table presented in this manuscript displays the topics addressed by the final 12 indicators. We have changed the topic of CQI4 from 'total (near-total) thyroidectomy' to 'extent of surgery'. Please see tracked changes in Table 1.

2. Table 2: In preoperative data items FNA is mentioned. Which system (Bethesda / THY) do the authors plan to use. Would they also consider using an ultrasound grading system?

We use Bethesda classification of thyroid cytology. We plan to consider entering ultrasonographic evaluation criteria according to an established system e.g. TIRADS.

3. In procedure they mention lymphovascular invasion and extra thyroidal extension. I wonder what exactly the group plan to collect. For example ETE will have to include macro versus micro if the 8th AJCC system is to be used. Also, lymphovascular invasion is very subjective. The categories yes/no may not be enough. no/suspicion/minimal (≤ 4)/extensive (>4) may be useful going forward.

For the data item 'presence of extrathyroidal extension' we are currently collecting the following responses: sternothyroid muscle or perithyroid soft tissues; subcutaneous soft tissues, larynx, trachea, oesophagus, or RLN; prevertebral fascia, encases carotid artery or mediastinal vessels; none; unknown. We are also collecting macro invasion, determined by surgeon during operation, and micro invasion, detected by pathologist.

With regard to the data item 'presence of lymphovascular invasion', we are currently collecting the following responses: yes; no; unknown. However, based on these reviewer comments we have expanded the responses to include: extensive (>4); minimal (≤ 4); suspicion; no; unknown.

4. For staging, if accurate path and surgical data is included, TN (not M) can be inferred.

T and N status can be established from accurate surgical and anatomical pathological data. The absence of distant metastases is often inferred from absence of positive evidence but the extent of the evaluation in the absence of clinical suspicion is often limited. In apparently low risk T and N categorization this is usual clinical practice.

5. Are the group planning to associate dates with the dynamic risk stratification data including Tg?

We plan to extend the database to longer follow-up at the conclusion of the pilot, once the current database is established, which should enable dynamic risk stratification involving use of imaging and serum thyroglobulin measurement.

6. In my version of figure 1 the opt-out final box overlaps the data collection box. This may be a glitch at my end but is worth checking

The figure has been updated accordingly.

VERSION 2 – REVIEW

REVIEWER	Glenn D. Braunstein, M.D. Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA
REVIEW RETURNED	03-Aug-2018

GENERAL COMMENTS	The authors have addressed my concerns. The major one concerning the components of patient care for individuals with thyroid cancer that enhance prognosis, decrease recurrence, improve survival (which for the most part is pretty good for most patients with thyroid cancer) cannot be adequately explored in a 90 day follow-up study. The authors have indicated that they plan on extending the follow-up period, gathering more information, and look at some of the current trends in practice that may alter outcomes (e.g. active surveillance). This will be very important and it would be nice to include a strong "promissory" note indicating that the plan would be to expand the registry to include follow-up for life, incorporation of endocrinologists, etc. This is a step in the right direction, but could "die" if stable, long-term funding is not forthcoming.
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REVIEWER	Iain Nixon NHS Lothian, Edinburgh, UK
REVIEW RETURNED	03-Aug-2018

GENERAL COMMENTS	I think the responses are satisfactory
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VERSION 2 – AUTHOR RESPONSE

Reviewer 1

The authors have addressed my concerns. The major one concerning the components of patient care for individuals with thyroid cancer that enhance prognosis, decrease recurrence, improve survival (which for the most part is pretty good for most patients with thyroid cancer) cannot be adequately explored in a 90 day follow-up study. The authors have indicated that they plan on extending the follow-up period, gathering more information, and look at some of the current trends in practice that may alter outcomes (e.g. active surveillance). This will be very important and it would be nice to include a strong "promissory" note indicating that the plan would be to expand the registry to include follow-up for life, incorporation of endocrinologists, etc. This is a step in the right direction, but could "die" if stable, long-term funding is not forthcoming.

As advised by reviewer 1 we have included a note following the discussion, titled 'Future Directions', which briefly outlines the plan to expand the registry.

Reviewer 2

I think the responses are satisfactory.

Thank you again for your consideration of this manuscript. Please do not hesitate to contact me should you require any further information.