Major Evolution in Clinical Detection of Thyroid Cancer Since 2000

Potential Impact on Findings and Analyses

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Medullary Thyroid Carcinoma Registry
In mice and rats, long-acting GLP-1 receptor agonists (GLP-1 RAs) caused proliferative and neoplastic changes in the thyroid C-cells.

As a Post Marketing PhV requirement, the FDA requested the sponsor of the first LA-GLP-1 RA (NN) to design and conduct an observational MTC Registry Study for at least 15 years.

Subsequently, all sponsors with FDA approved LA GLP-1 RAs have been required to conduct a similar 15 year registry of MTC incident cancers.
Formation of the MTC Registry Consortium

- As all sponsors would be pulling from the same very limited source, FDA suggested all Sponsors with LA GLP-1 RAs collaborate on 1 registry to minimize inconvenience to patients, physicians, and state cancer registries

- Thus the MTC Registry Consortium was formed

- United BioSource Corporation (UBC) is managing the MTC registry on behalf of the Sponsors

Kristine Harper, MD
March 22, 2016
Consortium Sponsors

- Consortium Sponsors include those companies with an FDA approved long-acting GLP-1RA and who have a contractual agreement to participate in the MTC Registry

- Current Members
  - Novo Nordisk (2010)
  - GlaxoSmithKline (10/2014)
  - Eli Lilly (2/2015)

- Other companies with long-acting GLP-1 RAs developed in the future could potentially join the Consortium

Kristine Harper, MD
March 22, 2016
1. To systematically monitor the annual incidence of MTC in the US through the North American Association of Central Cancer Registries (NAACCR) to identify any possible increase related to the introduction of long-acting GLP-1 RAs into the US market.
2. To establish a registry of incident cases of MTC in adults in the US to characterize their medical histories and possible risk factors, including history of long-acting GLP-1 RAs treatment.
Medullary Thyroid Carcinoma Registry

Figure 2. MTC Registry Paths to Collect Patient Data

**Patient Identification**
- **STATE CANCER REGISTRIES (SCRs)**
  - Twenty-eight SCRs provide newly reported cases of MTC to UBC via secure website or encrypted CD
  - Data collected on MTC cases diagnosed from January 1, 2010

**Exposure**
- **PATIENT**
  - SCR provides UBC with patient contact information
  - UBC/SCR/Physician consents patient
  - Patient completes telephone survey with UBC. Examples of data collected include comorbid conditions, history of diabetes, obesity and history of exposure to long-acting GLP-1 RAs.
  - Patients with diabetes and/or using a medication for weight management will have additional questions regarding long-acting GLP-1 RA use.

**Verification**
- **PHYSICIAN**
  - Based on state requirements, either UBC or SCR contacts the physician familiar with the patient's medical information.
  - Physician verification completed for MTC patients with diabetes or using a medication for weight management.

**Aggregate Data**
- **NAACCR (North American Association of Central Cancer Registries)**
  - NAACCR provides an annual aggregate data report on the incidence of MTC in the U.S.

Data stored in secure United BioSource Corporation (UBC) database.
Medullary Thyroid Carcinoma Registry

Figure 1. MTC Committees and Corporations Involved in the Conduct of the Registry

- **MTC Registry Consortium**: Sponsors with an Approved Long-acting GLP-1 Receptor Agonist with a Contractual Agreement with the MTC Registry
- **Registry Steering Committee**: Providing Scientific Leadership and Overall Governance
- **Registry Data Monitoring Committee**: Independent Evaluation of MTC Registry Data Makes Recommendations to the Consortium Sponsors
- **Administrative Committee**: Overall Administrative Management of MTC Registry Consortium
- **United BioSource Corporation**: Overall Management of the Registry on Behalf of the MTC Registry Consortium
As seen in Figure 1, the sponsors have formed the MTC Registry Consortium and partnered with the American Thyroid Association to conduct this registry under the management of the United BioSource Corporation. The Registry Committees provide scientific leadership and overall governance (Steering), an independent review of collected case data (Data Monitoring), and daily operational oversight (Administrative). To meet objective 1, annual MTC incidence rates are obtained from the North American Association of Central Cancer Registries (NAACCR). The time period prior to the introduction of long-acting GLP-1 RAs into the marketplace is used as the baseline (January 1, 2001 to December 31, 2009).

1. To meet objective 1, annual MTC incidence rates are obtained from the North American Association of Central Cancer Registries (NAACCR) using January 1, 2001 to December 31, 2009 as a baseline as it reflects the time period prior to the introduction of long-acting GLP-1 RAs into the marketplace.

2. To meet objective 2, new (or incident) cases of MTC after January 1, 2010 are identified by participating State Cancer Registries (SCRs). Once informed consent is obtained from the patient or proxy, a telephone interview is conducted to collect possible risk factors including comorbid conditions, history of diabetes, obesity, and history of exposure to long-acting GLP-1 RAs. If a patient was treated with a long-acting GLP-1 RA or had a diabetes diagnosis, attempts are made to contact the treating physician to obtain verification of diagnosis and medications prescribed.
Increasing Diagnosis of Subclinical Thyroid Cancers Leads to Spurious Improvements in Survival Rates

Allen S. Ho, MD; Louise Davies, MD; Iain J. Nixon, MD; Frank L. Palmer, MD; Laura Y. Wang, MD; Snehal G. Patel, MD; Ian Ganly, MD; Richard J. Wong, MD; R. Michael Tuttle, MD; and Luc G. T. Morris, MD, MSc

SEER 1975-2009
Age adjusted incidence rates per 100,000
Age-Period-Cohort Analysis of Thyroid Cancer Incidence in Korea

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<th>Histologic type</th>
<th>Year</th>
<th>APC(^a)</th>
<th>Difference</th>
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Women

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<tr>
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<th>Year</th>
<th>APC(^a)</th>
<th>Difference</th>
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</table>
310 patients had microMTC; its incidence increased during the study period (p trend= .033), and microMTC as a proportion of all MTCs increased by 39%. The mean tumor size was 5.7 mm.
MTC Prevalence at Autopsy 0.42%

If entire gland examined with Calcitonin Immunostain
Composite Prevalence In Post-Surgical Nodular Goiters

0.3%

15,992 patients
12 series
Age-Period-Cohort Analysis of Thyroid Cancer Incidence in Korea

Adjusted $r^2=0.90$
$p < 0.001$

Age standardized incidence rate per 100,000

Ultrasonographs per 100,000
Increased Thyroid Cancer Incidence Corresponds to Increased Use of Thyroid Ultrasound and Fine-Needle Aspiration: A Study of the Veterans Affairs Health Care System

Jose P. Zevallos, MD, MPH; Christine M. Hartman, PhD; Jennifer R. Kramer, MPH, PhD; Erich M. Sturgis, MD, MPH; and Elizabeth Y. Chiao, MD, MPH

Figure 1. These charts illustrate the changing numbers of (A) thyroid cancer diagnoses, (B) thyroid ultrasound tests, and (C) thyroid fine-needle aspiration tests from 2000 to 2012.
Increased Detection in the US

The Increasing Incidence of Thyroid Cancer: The Influence of Access to Care

Luc Morris et al, Thyroid 2013.
Age standardized incidence rates correlated
Density of Endocrinologists
Use of Neck Ultrasonography

Explained $\approx 50\%$ of the state level incidence
Changing Trends in the Incidence of Thyroid Cancer in the United States

Data are expressed per 100,000 persons and age-adjusted to the 2000 US population. Data markers represent observed incidence rates; lines, the joinpoint-modeled regression lines; and percentages, the annual percentage change (Table).
South Korea’s Thyroid-Cancer “Epidemic” — Turning the Tide

Figure 1. Trend in the Number of Operations for Thyroid Cancer in South Korea, 2001–2015. Data are from the Health Insurance Review and Assessment Service, South Korea.
Impact of Thyroid Cancer Guidelines

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer*

Bryan R. Haugen,1,4 Erik K. Alexander,2 Keith C. Bible,3 Gerard M. Doherty,4 Susan J. Mandel,5 Yuri E. Nikiforov,6 Furio Pacini,7 Gregory W. Randolph,8 Anna M. Sawka,9 Martin Schlumberger,10 Kathryn Schuff,11 Steven I. Sherman,12 Julie Ann Sosa,13 David L. Steward,14 R. Michael Tuttle,15 and Leonard Wartofsky16

Decrease in FNA diagnosis of Papillary Microcarcinoma
Observation of Papillary Microcarcinoma

No surgery, no pathology report, not counted in tumor registries

Haugen, Thyroid 2015
Non-invasive follicular variant papillary thyroid cancer

Renamed

Non-invasive thyroid follicular neoplasm with papillary like nuclear features (NIFT-P)
Clinically evident thyroid cancer
60,000 cases/year
Prevalence 600,000

Previously subclinical thyroid cancer

US Population
10-15% have PTC
0.4% have MTC

US Guided FNA

Ultrasound