Clinical Trials Planning Meeting (CTPM)

Head & Neck Cancer Steering Committee
Optimizing Individualized Treatment of Early Stage Thyroid Cancer
November 10-11, 2013
FAES Education Center, Building 10, NIH Campus
Bethesda, MD
Co-Chairs
Gary Clayman, DMD, MD, FACS & Matthew Ringel, MD

Introduction/ Meeting Description

The incidence of thyroid cancer has been increasing in the United States and has risen over 50% in the past 5 years. The largest percentage of these cancers are well-differentiated thyroid which have an excellent prognosis if detected early. There is a concern among clinicians – endocrinologists, oncologists, surgeons, that these early stage cancers are potentially being over-treated and treatment related morbidity is a potential evolving problem.

Invited attendees included surgeons, endocrinologist's oncologists, pathologists, radiation oncologists and patient advocates

The purpose of this meeting was to:

- Determine the feasibility and endpoints for a prospective clinical trial assessing the role of active surveillance vs. early surgical intervention of patients with intrathyroidal FNA-proven papillary thyroid cancer (PTC) without clinical or radiographic evidence of nodal metastases with power to achieve statistically robust conclusions.
- If surgery is needed for intrathyroidal PTC, should a "prophylactic" central neck dissection be performed in the absence of radiographic or intraoperative identification of local invasion or nodal metastases?
- Determine the feasibility and endpoints of a prospective clinical trial assessing the role of active surveillance vs. surgical intervention for confirmed, low volume residual or recurrent PTC in the neck.
- Define appropriate outcome measures for this population that are clinically relevant including quality of life measures, quality outcomes in surgery and local and regional control rates.
- Identify and address obstacles for the successful conduct of trials in this population including the need for multidisciplinary teams, the duration of follow-up necessary to reach specific endpoints, and the number of patients required for statistical significance to be achieved for selected endpoints.

- Discuss the possible role of biomarkers in this process and utilization of available genomic information that is in the literature or forthcoming from groups such as TCGA (The Cancer Genome Atlas) and others.

Background/Importance of Research Topic/Disease/Limitations

- Thyroid Cancer projected incidence in the United States for 2013 is 69,220 cases. This accounts for 4% of new cancer cases.
- The largest increase is in papillary thyroid cancer (PTC)
- Appropriate management of early stage thyroid cancer has become an issue of public heath importance as overtreatment of early stage thyroid cancer may be associated with certain morbidities and affect quality of life.
- The prognosis of PTC, in both early and advanced stages is excellent, particularly in patients <45 years old.
- Need to focus on optimal treatments for early stage disease to include, but not be limited to active surveillance vs. immediate surgery and systemic treatment.

Consensus & Recommendations

- *The CTPM leaders had the participants break out into 4 Working Groups:*

1. Primary Papillary Carcinomas: Active Surveillance vs. Surgery
2. Primary Papillary Thyroid Cancer: Extent of Initial Surgery
3. Residual or Recurrent Papillary Thyroid Cancer: Active Surveillance vs. Surgery or Other Local Therapy
4. Quality of Life Measures after Surgery or I-131 Therapy

<u>Recommendations from Group 1:</u>

Phase II Clinical Trial to examine the feasibility of comparing active surveillance with conventional surgical therapies in patients with intrathyroidal cT1 (<2cm), cN0 PTC in the U.S.

<u>Recommendations from Group II:</u>

Comprehensive central compartment neck dissection is safe and effective therapy in patients with cT1b-T3 N0 papillary thyroid carcinoma.

- *Secondary Endpoint: anatomic structural disease in central compartment*
- *Primary Endpoints: 1) Permanent/temporary (symptomatic) hypoparathyroidism 2) Permanent/temporary RLN dysfunction*
- *Patient Reported Outcomes & Quality of Life*

<u>Recommendations Group III:</u> Observational Study for Recurrent/Persistent Disease:

- *Frequency of progression (10% @3-5 years)*
- *Time to Progression*
- *Molecular Analysis – informed by TCGA*
- *Quality of Life – secondary endpoints*

<u>Recommendations Group IV: QoL Endpoints after Surgery:</u>

- *Integrate functional and global measures*
- *Use validated instruments (PROMIS, MDASI)*
- *Discussed development of decision aids*
- *Integration with survivorship clinics*
- *Specific QoL measures to be monitored:*
- *Voice – especially if thyroidectomy performed*
- *Parathyroid*
- *Swallowing – especially if thyroidectomy performed*
- *Fatigue*
- *Anxiety*
- *Body Image*
- *Oncofertility*
- *Financial*
- *Bone/Cardiovascular*

Also addressed- Having only surgeons who perform high volume of thyroid surgery be eligible to enter patients onto clinical trials

Cost Effective Analysis

TSH Suppression- downstream effects

Surveillance would be mandatory regardless of Rx (surgery/I-131)

Proposed Clinical Trial Concepts after discussion:

Trial 1

- Multiple arm trial for favorable papillary thyroid carcinomas, 2 cm or less in size.
    - Randomization will include an observation arm; thyroid lobectomy only; or a total thyroidectomy.
- The focus of this trial is to build upon what was initiated in published trials in Japan of observation in patients with favorable thyroid cancer.
- The trial is being proposed through ACRIN.
- The trial will develop parameters for observation, what is safe and not safe to observe.
- Despite a large body of evidence that will support less than total thyroidectomy; the NCCN guidelines propose total thyroidectomy for lesions 1.5 cm or greater, despite the fact that experts do not follow this.
- The trial would be at least 5 years in duration of follow up.
- There are published trials with over 300 patients with follow up greater than 5 years.

Trial 2

- The second trial that was proposed is a clinical trial that looks at randomization of favorable thyroid cancers, 1.5 cm or greater in size.
- Randomized between total thyroidectomy +/- prophylactic central compartment dissection.
- This trial was originally proposed through the VA Cooperative Group with Dr. Jeffrey Moley as the principal investigator.
- The trial will be controlled for radioactive iodine therapy.
- The number of patients will be based on the primary endpoints as it relates to complications of surgical intervention e.g. transient or permanent recurrent nerve paralysis and transient and persistent or long term hypo-parathyroidism.
- This trial will be conducted at the University of Wisconsin funded by an NIH-RO1 grant. Rebecca Sippel, M.D. is the PI.

This Executive Summary presents the consensus arising from the CTPM. These recommendations are not meant to address all clinical contexts, but rather represent priorities for publicly funded clinical research.

Next Steps or Anticipated Action(s)

The CTPM Co-Chairs, HNSC Co-Chairs, and NCI staff has been in discussions with ACRIN leadership and the VA. The study may end up as a study with the VA and associated university hospital systems so that the resources from the VA trial can remain the primary funding source of the trial. ECOG has also been approached to sponsor a surgical trial.

The presenters and co-chairs will prepare a manuscript from the proceedings to be submitted to the journal Thyroid.