



# American Head and Neck Society - Journal Club

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### AHNS Endocrine Section Edition

*This Issue of the AHNS Journal Club has been compiled and reviewed by members of the*

**AHNS Endocrine Section:**

**(Brendan C. Stack, Jr. MD, Chair &, Michael Singer MD, Vice-Chair)**

#### **Contributing Members:**

*Brendan C. Stack, Jr. MD,*

*Michael Singer MD,*

*Alvaro Sanabria MD, MSc, PhD,*

*Russell Smith, MD*

Dear Colleagues,

The AHNS *Endocrine Section* is pleased to present the issue of the AHNS Journal Club.

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## Complete Surgical Resection Following Neoadjuvant Dabrafenib Plus Trametinib in $BRAF^{V600E}$ -Mutated Anaplastic Thyroid Carcinoma

Jennifer R Wang, Mark E Zafereo, Ramona Dadu, Renata Ferrarotto, Naifa L Busaidy, Charles Lu, Salmaan Ahmed, Maria K Gule-Monroe, Michelle D Williams, Erich M Sturgis, Ryan P Goepfert, Neil D Gross, Stephen Y Lai, Gary Brandon Gunn, Jack Phan, David I Rosenthal, Clifton David Fuller, William H Morrison, Priyanka Iyer Maria E Cabanillas

From the *Thyroid*. August 2019.

**Background:** When achieved, complete surgical resection improves outcomes in anaplastic thyroid carcinoma (ATC). However, most ATC patients present with advanced inoperable disease, often with impending airway obstruction, increased hemorrhage risk, and significant dysphagia. Novel treatment strategies are critically needed to improve disease control and decrease locoregional morbidity. The objective of this study was to determine the feasibility and effectiveness of a neoadjuvant regimen by using dabrafenib with trametinib followed by surgical resection in patients with initially unresectable  $BRAF^{V600E}$ -mutated ATC.

**Methods:** Case series of six consecutive patients with  $BRAF^{V600E}$ -mutated ATC diagnosed between January 2017 and February 2018. Pathologic confirmation of ATC was obtained before treatment.  $BRAF^{V600E}$  status was ascertained via immunohistochemistry or sequencing of circulating tumor DNA. All patients received dabrafenib and trametinib (DT) followed by surgical resection and adjuvant chemoradiation. Three patients also received pembrolizumab.

**Results:** Complete surgical resection was achieved in all patients. Histopathologic analyses of resected specimens showed high pathologic response rates with significantly decreased ATC viability and residual papillary thyroid carcinoma components. Overall survival at six months and one year was 100% and 83%, respectively. Locoregional control rate was 100%. Two patients died of distant metastases without evidence of locoregional disease at 8 and 14 months from diagnosis. The remaining four patients had no evidence of disease at the last follow-up.

**Conclusions:** We report the first series in the literature of  $BRAF^{V600E}$ -mutated ATC patients with locoregionally advanced disease treated with DT followed by surgical resection. We demonstrated feasibility of complete resection, decreased need for tracheostomy, high pathologic response rates, and durable locoregional control with symptom amelioration.

### Summary Statements

- Cases series which describes a multidisciplinary approach for patients with anaplastic thyroid cancer based upon the presence of BRAF-V600E mutation
- Patients with unresectable anaplastic thyroid cancer underwent neoadjuvant therapy with targeted agents followed by surgical resection of residual disease and adjuvant concurrent chemoradiation therapy
- 2/3 of cohort had no evidence of disease at last follow-up and patients that died of disease had distant progression with durable locoregional control



### Strengths

- Well-defined patient cohort with rare disease which is typically considered incurable treated with a standardized approach with favorable results
- Detailed summary of treatment including surgical findings as well as surgical pathology from resection provided

### Weaknesses

- Cases series with small number of patients
- Relatively short observation period of 1-2 years for entire cohort

## [Radiofrequency ablation and related ultrasound-guided ablation technologies for treatment of benign and malignant thyroid disease: An international multidisciplinary consensus statement of the American Head and Neck Society Endocrine Surgery Section with the Asia Pacific Society of Thyroid Surgery, Associazione Medici Endocrinologi, British Association of Endocrine and Thyroid Surgeons, European Thyroid Association, Italian Society of Endocrine Surgery Units, Korean Society of Thyroid Radiology, Latin American Thyroid Society, and Thyroid Nodules Therapies Association.](#)

*Orloff LA, Noel JE, Stack BC Jr, Russell MD, Angelos P, Baek JH, Brumund KT, Chiang FY, Cunnane MB, Davies L, Frasoldati A, Feng AY, Hegedüs L, Iwata AJ, Kandil E, Kuo J, Lombardi C, Lupo M, Maia AL, McIver B, Na DG, Novizio R, Papini E, Patel KN, Rangel L, Russell JO, Shin J, Shindo M, Shonka DC Jr, Karcioglu AS, Sinclair C, Singer M, Spiezia S, Steck JH, Steward D, Tae K, Tolley N, Valcavi R, Tufano RP, Tuttle RM, Volpi E, Wu CW, Abdelhamid Ahmed AH, Randolph GW.*

*From the **Head Neck**. March 2022.*

**Background:** The use of ultrasound-guided ablation procedures to treat both benign and malignant thyroid conditions is gaining increasing interest. This document has been developed as an international interdisciplinary evidence-based statement with a primary focus on radiofrequency ablation and is intended to serve as a manual for best practice application of ablation technologies.

**Methods:** A comprehensive literature review was conducted to guide statement development and generation of best practice recommendations. Modified Delphi method was applied to assess whether statements met consensus among the entire author panel.

**Results:** A review of the current state of ultrasound-guided ablation procedures for the treatment of benign and malignant thyroid conditions is presented. Eighteen best practice recommendations in topic areas of preprocedural evaluation, technique, postprocedural management, efficacy, potential complications, and implementation are provided.

**Conclusions:** As ultrasound-guided ablation procedures are increasingly utilized in benign and malignant thyroid disease, evidence-based and thoughtful application of best practices is warranted.



Best Practices (abbreviated):

- 1. US-guided ablation procedures may be used as a first-line alternative to surgery for patients with benign thyroid nodules...
- 2. Thermal ablation procedures can be a safe therapeutic alternative in patients with an autonomously functional thyroid nodule...
- 3. US-guided ablation procedures may be considered in patients with suitable primary papillary microcarcinoma, in patients with suitable recurrent papillary thyroid carcinoma, and preprocedural biochemical and imaging assessment aid in determining curative versus palliative treatment...
- 4. Subjective voice assessment should be undertaken prior, patients with voice impairment or relevant prior surgical history warrant a laryngeal evaluation, laryngeal exam should be performed prior to ablation on the contralateral side after ipsilateral ablation.
- 5. Complete radiographic, biochemical, medical, and symptomatic evaluation should be performed and discussion should be held with the patient regarding expected outcome(s) and potential risks.
- 6. When patient comorbidities and disposition permit...local anesthesia allows for monitoring of periprocedural complications.
- 7. Hydrodissection creates distance between the target lesion and vital structures...
- 8. Utilization of the moving shot technique via the transisthmic approach and delivery of energy only when the needle tip is visualized... And the moving shot technique via the transisthmic approach minimizes inadvertent thermal injury to surrounding critical structures.
- 9. ...established guidelines for procedural sedation in adults should be followed if sedation is administered.
- 10. Immediate ... assessment of acute complications ... is required.
- 11. Subjective voice assessment should be undertaken ... following ablation..., changes in voice ... require laryngeal evaluation...
- 12. Careful documentation of ... metrics before treatment and during the follow up ...
- 13. ...primary objective measures of efficacy include ultrasonographic measurement ... and preservation or normalization of thyroid function, patient-reported outcomes, including validated symptom, cosmetic, and quality of life instruments ... repeat ablation of a benign nodule can be considered for remnant nodular tissue..., retreatment for persistent hyperthyroidism may be performed.
- 14. Following thermal ablation for recurrent malignancy, ultrasonographic determination of tumor volume, assessment of locoregional disease status, and serum Tg/TgAb are performed ...
- 15 ... sonographic volume reduction or complete resolution of the malignant lesion, ..., are necessary to determine oncologic effect.



- 16. Assiduous recording of complications ...
- 17. Prior to performing any US-guided thermal ablation procedure, advanced training in and facility with US of the thyroid and neck are essential, proficiency with US-guided fine needle aspiration biopsies of thyroid nodules is recommended, ..., the provider should receive specific instruction on the chosen ablation technique..., and optimal practice involves one's initial cases being supervised by a physician experienced in US-guided ablation procedures.
- 18. Physicians ... should communicate and facilitate long-term follow-up...

Why was this article selected? The topic of thyroid nodule ablation is the premier and contemporary issue of our section presently and this paper highlights the work and focus of our section on emerging technology. Additionally, this paper highlights the global reach of this topic and demonstrates the section's collaboration with sister professional societies around the globe. These efforts bear fruit in the quality of the publication as well as future professional interchanges and collaborations.

**Strengths:**

This article provides a comprehensive introduction of ablative technology to the head and neck surgical community. It also lays a foundation for a coordinated implementation of ablative technology into a clinical practice.

**Weaknesses:**

This article is written generically about ablation and is not specific to the many particular ablative technologies in current clinical use. This article presents statements based on expert consensus and IS NOT a practice guideline or systematic review.

**Evaluating the Rising Incidence of Thyroid Cancer and Thyroid Nodule Detection Modes: A Multinational, Multi-institutional Analysis**

*Sajisevi M, Caulley L, Eskander A, Du YJ, Auh E, Karabachev A, Callas P, Conradie W, Martin L, Pasternak J, Golbon B, Rolighed L, Abdelhamid Ahmed AH, Badhey A, Cheung AY, Corsten M, Forner D, Liu JC, Mavedatnia D, Meltzer C, Noel JE, Patel V, Sharma A, Tang AL, Tsao G, Venkatramani M, Williams M, Wrenn SM, Zafereo M, Stack BC Jr, Randolph GW, Davies L.*

*From the JAMA Otolaryngol Head Neck Surg. September 2022.*

**Importance:** There is epidemiologic evidence that the increasing incidence of thyroid cancer is associated with subclinical disease detection. Evidence for a true increase in thyroid cancer incidence has also been identified. However, a true increase in disease would likely be heralded by an increased incidence of thyroid-referable symptoms in patients presenting with disease.

**Objectives:** To evaluate whether modes of detection (MODs) used to identify thyroid nodules for surgical removal have changed compared with historic data and to determine if MODs vary by geographic location.

**Design, setting, and participants:** This was a retrospective analysis of pathology and medical records of 1328 patients who underwent thyroid-directed surgery in 16 centers in 4 countries: 4 centers in Canada, 1 in Denmark, 1 in South Africa, and 12 in the US. The participants were the first 100 patients (or the largest number available) at each center who had thyroid surgery in 2019. The MOD of the thyroid finding that required surgery was classified using an updated version of a previously validated tool as endocrine condition, symptomatic thyroid, surveillance, or without thyroid-referable symptoms (asymptomatic). If asymptomatic, the MOD was further classified as clinician screening examination, patient-requested screening, radiologic serendipity, or diagnostic cascade.

**Main outcomes and measures:** The MOD of thyroid nodules that were surgically removed, by geographic variation; and the proportion and size of thyroid cancers discovered in patients without thyroid-referable symptoms compared with symptomatic detection. Data analyses were performed from April 2021 to February 2022.

**Results:** Of the 1328 patients (mean [SD] age, 52 [15] years; 993 [75%] women; race/ethnicity data were not collected) who underwent thyroid surgery that met inclusion criteria, 34% (448) of the surgeries were for patients with thyroid-related symptoms, 41% (542) for thyroid findings discovered without thyroid-referable symptoms, 14% (184) for endocrine conditions, and 12% (154) for nodules with original MOD unknown (under surveillance). Cancer was detected in 613 (46%) patients; of these, 30% (183 patients) were symptomatic and 51% (310 patients) had no thyroid-referable symptoms. The mean (SD) size of the cancers identified in the symptomatic group was 3.2 (2.1) cm (median [range] cm, 2.6 [0.2-10.5]; 95% CI, 2.91-3.52) and in the asymptomatic group, 2.1 (1.4) cm (median [range] cm, 1.7 [0.05-8.8]; 95% CI, 1.92-2.23). The MOD patterns were significantly different among all participating countries.

**Conclusions and relevance:** This retrospective analysis found that most thyroid cancers were discovered in patients who had no thyroid-referable symptoms; on average, these cancers were smaller than symptomatic thyroid cancers. Still, some asymptomatic cancers were large, consistent with historic data. The substantial difference in MOD patterns among the 4 countries suggests extensive variations in practice.

Why was this article selected? Two reasons: The topic of thyroid nodule and cancer detection is a contemporary issue that has impacted patients world-wide with issues of screening, treatment options, and complications from treatment received. This paper highlights the work and focus of our section on topics of contemporary clinical concern for our section members. Additionally, this paper highlights the global reach of this topic and demonstrates the section's collaboration with centers around the globe. These efforts bear fruit in the quality of the publication as well as the opportunity for future professional interchanges and collaborations.

- Most thyroid cancers were discovered in patients who had no thyroid-referable symptoms; on average, these cancers were smaller than symptomatic thyroid cancers.
- There is epidemiologic evidence that the increasing incidence of thyroid cancer is associated with subclinical disease detection.
- Modes of detection (MODs) used to identify thyroid nodules for surgical removal have changed.



- The MOD of the thyroid finding that required surgery was classified as endocrine condition, symptomatic thyroid, surveillance, or asymptomatic. When asymptomatic, the MOD was further classified as screening, patient-requested, incidental on radiology, or as part of a diagnostic cascade.
- 34% (448) of the surgeries were for patients with thyroid-related symptoms, 41% (542) for thyroid findings discovered without symptoms, 14% (184) for endocrine conditions, and 12% (154) for nodules with original MOD unknown (under surveillance).
- Cancer was detected in 613 (46%) patients; of these, 30% were symptomatic and 51% had no thyroid-referable symptoms.
- The mean (SD) size of the cancers identified in the symptomatic group was 3.2 (2.1) cm (median) and in the asymptomatic group, 2.1 (1.4) cm (median).
- The MOD patterns were significantly different among all participating countries.
- The substantial difference in MOD patterns among the 4 countries suggests extensive geographic variations in practice.

**Strengths:** This article reports how thyroid nodules and thyroid cancers are found in clinical practice with highlighting of geographic differences in clinical practice. Validation that most thyroid cancers diagnosed are asymptomatic and are smaller than those found in symptomatic individuals is beneficial.

**Weaknesses:** This is a retrospective study with sporadically selected institutions. A systematic study design to include a uniformly disperse geography of participating institutions would make data more universal. Prospective collection of this data through a well-designed registry would be optimal.

### **[American Head and Neck Society Endocrine Surgery Section and International Thyroid Oncology Group consensus statement on mutational testing in thyroid cancer: Defining advanced thyroid cancer and its targeted treatment.](#)**

*Shonka DC Jr, Ho A, Chintakuntlawar AV, Geiger JL, Park JC, Seetharamu N, Jasim S, Abdelhamid Ahmed AH, Bible KC, Brose MS, Cabanillas ME, Dabekaussen K, Davies L, Dias-Santagata D, Fagin JA, Faquin WC, Ghossein RA, Gopal RK, Miyauchi A, Nikiforov YE, Ringel MD, Robinson B, Ryder MM, Sherman EJ, Sadow PM, Shin JJ, Stack BC Jr, Tuttle RM, Wirth LJ, Zafereo ME Jr, Randolph GW.*

*From the **Head Neck**. June 2022.*

**Background:** The development of systemic treatment options leveraging the molecular landscape of advanced thyroid cancer is a burgeoning field. This is a multidisciplinary evidence-based statement on the definition of advanced thyroid cancer and its targeted systemic treatment.

**Methods:** An expert panel was assembled, a literature review was conducted, and best practice statements were developed. The modified Delphi method was applied to assess the degree of consensus for the statements developed by the author panel.



**Results:** A review of the current understanding of thyroid oncogenesis at a molecular level is presented and characteristics of advanced thyroid cancer are defined. Twenty statements in topics including the multidisciplinary management, molecular evaluation, and targeted systemic treatment of advanced thyroid cancer are provided.

**Conclusions:** With the growth in targeted treatment options for thyroid cancer, a consensus definition of advanced disease and statements regarding the utility of molecular testing and available targeted systemic therapy is warranted.

### Summary Statements

Expert author consensus statement on the utility of somatic genetic alterations for prognosis and therapeutic intervention in advanced thyroid cancer.

- Developed under the auspices of the American Head and Neck Society (AHNS) Endocrine Surgical Section and the International Thyroid Oncology Group (ITOG).
- In thyroid cancer somatic mutational testing should employ multiplexed NGS-based panels assays that include testing for gene fusions rather than multiple single-gene tests.
- To search for therapeutic targets somatic mutational testing for RET, NTRK1, NTRK3, and ALK gene fusions should be performed on patients with advanced DTC, that tested negative for BRAF V600E.
- Multikinase inhibitors or inhibitors specific for BRAF, RET, or NTRK mutations should be offered for the treatment of patients with progressive or symptomatic advanced differentiated thyroid carcinoma.
- All patients with medullary thyroid carcinoma should be for tested germline RET mutations.
- In anaplastic cancer BRAF V600E rapid testing mutational status should be obtained.
- Comprehensive somatic mutational testing of all anaplastic carcinomas should be mandatory at diagnosis.
- Combination dabrafenib and trametinib therapy may be used for resectable anaplastic carcinoma and should be promptly started in patients with unresectable ATC when BRAF V600E mutations are found.

### Strengths

- Multidisciplinary expert author panel with extensive clinical, laboratory, and research knowledge of advanced thyroid cancers.
- Cutting edge review of mutational testing for advanced thyroid cancer.

### Weaknesses

- Systematic review and meta-analysis not performed.
- Limited data available to support more definitive statements.





## **Association of Autofluorescence-Based Detection of the Parathyroid Glands During Total Thyroidectomy with Postoperative Hypocalcemia Risk: Results of the PARAFLUO Multicenter Randomized Clinical Trial**

*Benmiloud F, Godiris-Petit G, Gras R, Gillot JC, Turrin N, Penaranda G, Noullet S, Chéreau N, Gaudart J, Chiche L, Rebaudet S.*

*From the JAMA Surg. February 2020.*

**Importance:** Because inadvertent damage of parathyroid glands can lead to postoperative hypocalcemia, their identification and preservation, which can be challenging, are pivotal during total thyroidectomy.

**Objective:** To determine if intraoperative imaging systems using near-infrared autofluorescence (NIRAF) light to identify parathyroid glands could improve parathyroid preservation and reduce postoperative hypocalcemia.

**Design, setting, and participants:** This randomized clinical trial was conducted from September 2016 to October 2018, with a 6-month follow-up at 3 referral hospitals in France. Adult patients who met eligibility criteria and underwent total thyroidectomy were randomized. The exclusion criteria were preexisting parathyroid diseases.

**Interventions:** Use of intraoperative NIRAF imaging system during total thyroidectomy.

**Main outcomes and measures:** The primary outcome was the rate of postoperative hypocalcemia (a corrected calcium <8.0 mg/dL [to convert to mmol/L, multiply by 0.25] at postoperative day 1 or 2). The main secondary outcomes were the rates of parathyroid gland autotransplantation and inadvertent parathyroid gland resection.

**Results:** A total of 245 of 529 eligible patients underwent randomization. Overall, 241 patients were analyzed for the primary outcome (mean [SD] age, 53.6 [13.6] years; 191 women [79.3%]); 121 who underwent NIRAF-assisted thyroidectomy and 120 who underwent conventional thyroidectomy (control group). The temporary postoperative hypocalcemia rate was 9.1% (11 of 121 patients) in the NIRAF group and 21.7% (26 of 120 patients) in the control group (between-group difference, 12.6% [95% CI, 5.0%-20.1%];  $P = .007$ ). There was no significant difference in permanent hypocalcemia rates (0% in the NIRAF group and 1.6% [2 of 120 patients] in the control group). Multivariate analyses accounting for center and surgeon heterogeneity and adjusting for confounders, found that use of NIRAF reduced the risk of hypocalcemia with an odds ratio of 0.35 (95% CI, 0.15-0.83;  $P = .02$ ). Analysis of secondary outcomes showed that fewer patients experienced parathyroid autotransplantation in the NIRAF group than in the control group: respectively, 4 patients (3.3% [95% CI, 0.1%-6.6%]) vs 16 patients (13.3% [95% CI, 7.3%-19.4%];  $P = .009$ ). The number of inadvertently resected parathyroid glands was significantly lower in the NIRAF group than in the control group: 3 patients (2.5% [95% CI, 0.0%-5.2%]) vs 14 patients (11.7% [95% CI, 5.9%-17.4%]), respectively;  $P = .006$ ).

**Conclusions and relevance:** The use of NIRAF for the identification of the parathyroid glands may help improve the early postoperative hypocalcemia rate significantly and increase parathyroid preservation after total thyroidectomy.

**Summary Statement:**

- Randomized clinical trial of 241 adults, treated with thyroidectomy with or without a NIRAF imaging device to aid in parathyroid gland identification.
- Use of NIRAF during total thyroidectomy helped lower the temporary postoperative hypocalcemia rate from 22% to 9%.
- Patients undergoing NIRAF assisted surgery had statistically lower rates of parathyroid gland incidental resection and autotransplantation.

**Strengths**

- Well designed, randomized control trial.
- Demonstrates the potential power of this innovative technology.

**Weaknesses**

- Limited sample size.
- Employs questionable definition for long term hypocalcemia which may serve as a confounding factor

**[Association of Multifocality with Prognosis of Papillary Thyroid Carcinoma: A Systematic Review and Meta-analysis](#)**

*Hyeonkyeong Kim, Hyungju Kwon, Byung-In Moon*

*From the JAMA Otolaryngol Head Neck Surg. October 2021.*

**Importance:** Multifocality is common in papillary thyroid carcinoma (PTC), but it is unclear whether multifocal tumors are associated with tumor recurrence or cancer-specific survival.

**Objective:** To compare tumor recurrence rates in patients with multifocal vs unifocal PTCs.

**Data Sources:** We searched PubMed, SCOPUS, Web of Science Core Collection, and Cochrane Database of Systematic Reviews for pertinent studies published in English from inception to June 30, 2020.

**Study Selection:** The search strategy yielded 26 studies that compared tumor recurrence in patients with multifocal vs unifocal PTC.

**Data Extraction and Synthesis:** Data was extracted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline. Characteristics of study populations and hazard ratio (HR) of multifocality were independently extracted by 2 investigators.

**Main Outcomes and Measures:** The primary outcome was tumor recurrence and the secondary outcome was cancer-specific survival. Subgroup analysis of the primary outcome was based on primary tumor size, number of tumor foci, and patient age.

**Results:** Among 26 studies with a total of 33 976 patients, recurrence rates were significantly higher in patients with multifocal PTC than in those with unifocal PTC (pooled HR, 1.81; 95% CI, 1.52–2.14). Cancer-specific survival was comparable between the groups (HR, 1.19; 95% CI, 0.85–1.68). In subgroup analyses, the HRs of multifocality for recurrence were associated with primary tumor size (HRs for PTC  $\leq 1$  cm and  $>1$  cm were 1.81 and 1.90, respectively), number of tumor foci (HRs for 2 foci and  $\geq 3$  foci were 1.45 and 1.95, respectively), and patient age (HRs for pediatric and adult patients were 3.19 and 1.89, respectively).

**Conclusions and Relevance:** This systematic review with meta-analysis found that multifocality was significantly associated with an increased risk of recurrence in patients with PTC, while cancer-specific survival showed no difference. Differences in tumor size, number of tumor foci, and patient age should be considered when interpreting the multifocality and the risk of recurrence.

### **Summary Statement:**

This systematic review and meta-analysis included 26 studies with 33 976 patients and found that multifocality was significantly associated with an increased risk of tumor recurrence.

### **Strengths**

- This review followed the methodological recommendations of PRISMA guidelines
- Search was comprehensive and statistical analysis was adequate
- Attempts to adjust results and explore heterogeneity causes using subgroup analysis were done.

### **Weaknesses**

- Most included studies were retrospective which can introduce selection bias.
- Methodological quality of studies was measured with Newcastle-Ottawa Scale which overestimate the quality of studies. Today, other more comprehensive tools as ROBINS are available and offer more accurate information.
- Authors found important statistical and clinical heterogeneity. Therefore, results should be evaluated with caution.

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