Annales d'Endocrinologie 86 (2025) 101734

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Letter to the editor

## Key data from the 2024 European Thyroid Association annual congress: What's new in aggressive thyroid carcinoma?

The 46th Annual Congress of the European Thyroid Association (ETA) was held in Athens, Greece, from September 7 to 10, 2024. Out of a rich and dynamic scientific program, the present *Letter to the Editor* offers an overview of data on aggressive thyroid cancer.

### 1. Current advances in aggressive and radioactive iodine-refractory follicular-derived thyroid cancer

#### *1.1. Prognostic impact of the 2022 WHO (World Health Organization) reclassification of oncocytic and follicular thyroid carcinoma*

Over the past two decades, incidence has steadily increased for differentiated thyroid carcinoma (DTC), and primarily papillary thyroid carcinoma (PTC), while other subtypes remained stable. Follicular thyroid carcinoma (FTC) accounts for 5–10% of cases, whereas oncocytic thyroid carcinoma (OTC) is rarer (3–5%). Both are typically treated by total thyroidectomy and radioactive iodine (RAI), with 10-year disease-specific survival (DSS) of 80–94%.

Until 2017, OTC was classified as a subtype of FTC, but the 2017 WHO classification of thyroid neoplasms redefined it as a separate entity, due to its distinct genetic profile and clinical behavior, including lower RAI-responsiveness. The 2017 classification also redefined FTC subtypes based on vascular invasion and survival, and added an encapsulated angio-invasive FTC subtype (EA-FTC) to the two subtypes defined in the 2004 classification: minimally invasive FTC (MI-FTC) and widely invasive FTC (WI-FTC). The 2022 classification extended these changes to OTC, with the same 3 subtypes: MI-OTC, EA-OTC and WI-OTC.

During the 2024 ETA congress, Stegenga et al., in a retrospective study, reported the prognostic impact of the 2022 reclassification of OTC and FTC [1]. After tumor revision by 2 independent pathologists, 15 OTCs (8 WI-OTCs and 7 MI-OTCs) out of 52 (28.8%) were reclassified as EA-OTC, and 34 FTCs (14 WI-FTCs and 20 MI-FTCs) out of 89 (38.2%) were reclassified as EA-FTC. The subgroup of encapsulated angio-invasive carcinomas accounted for approximately one-third of OTCs or FTCs. The 2022 WHO classification substantially improved risk stratification for DSS. Ten-year DSS rates were 100% for MI-OTC, 92.9% for EA-OTC and 56.5% for WI-OTC, compared to 100% for MI-OTC and 64.2% for WI-OTC on the 2004 WHO classification. Similar trends were observed for FTC, resulting in 10-year DSS rates of 100%, 93.3%, and 85% for MI-FTC, EA-FTC, and WI-FTC, respectively compared to 98.1% and 87.9% for MI-FTC and WI-FTC following the 2004 WHO classification. Prognosis for encapsulated angio-invasive carcinomas is different from the other two subgroups, but closer to that of the minimally invasive subgroup.

The 2022 WHO classification also improved risk stratification for RAI-refractory (RAIR) disease, compared to the 2004 edition. Ten-year incidence of RAIR disease on the 2022 classification was 25%, 41.2% and 52.9% for MI-OTC, EA-OTC and WI-OTC, respectively, and for MI-FTC, EA-FTC and WI-FTC, 5.1%, 6.3% and 50.3%, respectively.

#### *1.2. BRAF is 20!*

Since the discovery of the $BRAF^{V600E}$ mutation in thyroid cancer by Kimura et al. [2], significant advances have been made in understanding its role in disease pathophysiology, prognosis and therapeutic implications. This mutation is highly prevalent in PTC and leads to constitutive activation of the MAPK signaling pathway, playing a crucial role in tumorigenesis.

The $BRAF^{V600E}$ mutation is associated with stronger activation of the MAPK pathway, which contributes to tumor progression and more dedifferentiation [3]. This hyperactivation leads to a loss of iodine uptake ability in thyroid cancer cells, a key factor in resistance to RAI therapy. While *BRAF* mutation alone does not completely explain dedifferentiation, it is a significant contributing factor when associated with other molecular abnormalities [4]. It is also not the sole driver of poor prognosis, but rather part of a broader landscape of mutations influencing disease progression [3,4]. Laschinsky et al. demonstrated that additional molecular abnormalities, including *TERT* promoter and *TP53* mutations, are linked to the onset of RAI-refractoriness, underscoring the complex interplay of genetic events leading to resistance [4]. Other studies highlighted that the combination of *BRAF* mutations with other abnormalities leads to more aggressive tumor behavior and lower overall survival (OS) [3].

The identification of $BRAF^{V600E}$ provided new insights for targeted therapies. In RAIR DTC, one promising approach is redifferentiation therapy, which aims to restore uptake in RAI-refractory disease. Leboulleux et al., in the MERAIODE phase-II trial, including 21 patients with *BRAF*-mutated metastatic RAIR thyroid cancer, demonstrated that a combination of 42 days' dabrafenib and trametinib significantly improved RAI uptake [5], seen in 20 of the 21 patients (95.2%) on posttreatment whole-body scan. Furthermore, the 6-month evaluation found partial response (PR) in 38%, stable disease (SD) in 52%, and progressive disease (PD) in 10%. An independent cohort of the MERAIODE trial, including 10 patients with metastatic RAIR RAS-mutated thyroid cancer, also showed the effectiveness of this strategy with trametinib, but with slightly poorer results [6]. Six out of 10 patients (60%) showed RAI reuptake on posttreatment whole-body scan, although 30% already showed uptake in some lesions at baseline. The 6-month evaluation found 2 PRs, 7 SDs and 1 PD.

For patients with *BRAF*-mutated anaplastic thyroid cancer (ATC), targeted therapies have shown remarkable efficacy. Initially, the ROAR basket study reported that a combination of dabrafenib and trametinib led to significant therapeutic response in almost all the

https://doi.org/10.1016/j.ando.2025.101734
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histological types of cancer in the study, including ATC [7]. Real-world data on ATC patients subsequently confirmed these findings. Nunes Da Silva et al. reported a study of 27 ATC patients, divided into 3 groups: *BRAF*$^{V600E}$ treated with dabrafenib and trametinib, *BRAF* wild-type under multimodal therapy, and *BRAF* wild-type under compassionate care. OS was 475 days for the dabrafenib and trametinib group, 156 days for multimodal therapy, and 39 days for compassionate care ($P < 0.001$) [8]. More recently, Elisei et al., at the 2024 ETA congress, presented results of a retrospective study in 8 Italian centers, including 19 ATC patients receiving dabrafenib and trametinib [9]. Overall response rate was 74% (14 PRs), with SD in 3 patients and PD in 2 at first evaluation. Median OS was 21 months. Median progression-free survival (PFS) for naïve and pretreated patients was 8.3 and 3.6 months, respectively. Treatment was well tolerated, with the most common grade ≥ 3 adverse events being fever (15%), diarrhea (5%) and pneumonia (5%).

### *1.3. Effect of scheduled lenvatinib drug holidays in treatment of refractory differentiated thyroid cancer*

Since the SELECT phase-III trial, lenvatinib has become the first-line treatment for progressive RAIR-DTC [10]. However, it shows considerable toxicity, like other multitarget and antiangiogenic therapies, leading to frequent dose reduction or discontinuation. Alternating treatment periods and holidays was recently proposed, to achieve similar efficacy with fewer side-effects.

In 2024, Tahara et al. published a prospective observational study in which 253 patients with RAIR-DTC were treated with lenvatinib at an initial dose of 24 mg daily in a real-world clinical setting. Dose modification for toxicity was permitted, as were scheduled drug holidays to avoid severe or intolerable toxicity. Seventy-three of the patients had drug holidays, at the discretion of the attending physician, all after onset of severe or intolerable adverse events. The most common initial treatment schedule was a 14-day-on/7-day-off cycle. At data cutoff, 1-year OS in the overall population was 85.6%. More importantly, OS and PFS were significantly longer in patients with drug holidays than in those without: 95.8% vs. 81.5% 1-year OS (HR: 0.311; 95% CI: 0.132–0.732; $P = 0.0047$) and 94.5% vs. 83.5% 1-year PFS (HR: 0.307; 95% CI: 0.108–0.873; $P = 0.0190$). In addition, the drug holiday group had a significantly longer duration of lenvatinib administration at ≥ 10 mg per day ($P = 0.0363$) [11].

## 2. What is new in metastatic medullary thyroid carcinoma?

### *2.1. Is primary tumor resection in distant metastatic medullary thyroid carcinoma still a question?*

Medullary thyroid carcinoma (MTC) is a rare and aggressive form of thyroid cancer that can present with distant metastases at diagnosis. The benefit of primary tumor resection (PTR) in patients with metastatic MTC is debated. Two recent studies presented at the 2024 ETA congress, by Tao et al. [12] and by Liu et al. [13], examined the impact of PTR on survival in patients with metastatic MTC, using large-scale population-based data and advanced statistical methods to minimize selection bias.

Tao et al. [12] conducted a retrospective cohort study using the US National Cancer Institute SEER (Surveillance, Epidemiology and End Results) database, applying propensity score matching (PSM) to compare survival between patients undergoing PTR and not. Out of 238 distant metastatic MTC cases, 122 (51.3%) underwent PTR and showed significantly better OS and DSS than the non-surgical group, both before and after PSM. Median DSS was 85 months for the surgical group, versus 15 months for the non-surgical group. Median OS was 56 months and 10 months, respectively. Subgroup analyses suggested that all patients significantly benefited from PTR, except for those aged ≥ 65 years or with tumor ≤ 20 mm or > 1 metastasis sites.

Similarly, Liu et al. analyzed metastatic MTC. One hundred and five of the 186 patients (56.45%) underwent PTR [13], and this group showed lower overall mortality and cancer-specific mortality ($P < 0.05$). The authors also suggested that PTR significantly lowered the risk of overall mortality and cancer-specific mortality for patients with bone, lung, liver, or distant lymph node involvement (all $P < 0.05$) compared to those with brain metastases. Additionally, in patients with 1 or 2 metastatic organs, surgical resection was significantly associated with favorable overall survival ($P = 0.008$) and cancer-specific survival ($P = 0.0247$) compared to those with more than 2 metastatic organs.

### *2.2. Clinical utility of circulating tumoral DNA analysis for monitoring treatment in advanced sporadic medullary thyroid carcinoma*

Plasma circulating tumoral DNA is obtained by liquid biopsies in patients with tumors driven by oncogenic mutation. Analysis can identify and quantify genetic abnormalities underlying response or resistance during targeted therapy and thus improve management. Few data, however, are available for MTC patients.

Ciampi et al. studied 8 multi-metastatic MTC patients harboring either *RET* ($n = 7$) or *HRAS* ($n = 1$) mutations in tumoral tissue [14]. The patients were treated with selpercatinib, a RET inhibitor ($n = 6$), or a multi-kinase inhibitor (MKI) ($n = 2$). All patients showed stable disease during therapy. Plasma samples were collected before start of therapy and at 4 time-points during follow-up. The driver mutation was detected in 5 of the 8 RET-positive patients, and allelic frequency values dropped during therapy, showing a good correlation with disease status and serving as an additional biomarker for disease monitoring. Other pathogenic mutations in *ESR1*, *TP53* and *GNAS*, not previously detected in tumoral tissue, were found at low allelic frequency in the plasma of 5 patients, suggesting the presence of other subclones that may emerge during treatment. The authors suggested that these additional mutations may contribute to disease progression and could provide additional actionable targets.

## Disclosure of interest

The authors declare that they have no competing interest.

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