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## Efficacy of anlotinib combined with radioiodine to treat scalp metastasis of papillary thyroid cancer: A case report and review of literature

Li-Yong Zhang, Shao-Jun Cai, Bo-Yan Liang, Shou-Yi Yan, Bo Wang, Meng-Yao Li, Wen-Xin Zhao

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### Abstract

#### BACKGROUND

Papillary thyroid cancer (PTC) is one of the well-differentiated thyroid tumors. Cutaneous metastasis from differentiated thyroid cancers occurs in < 1% of primary thyroid carcinomas but produces the worst survival prognosis. The multi-targeting tyrosine kinase inhibitor anlotinib has been approved to treat refractory advanced non-small-cell lung cancer as well as advanced soft-tissue and clear cell sarcomas in China.

#### CASE SUMMARY

In a patient with scalp metastasis caused by PTC, thyroid and skull metastasis tumor sizes were significantly reduced after a trial of neoadjuvant anlotinib therapy for 3 cycles. Anlotinib maintenance medication after thyroidectomy further reduced the metastatic skull tumor size thereby preventing the requirement for craniotomy.

#### CONCLUSION

The outcome of the present trial confirmed the potential of anlotinib therapy to treat scalp metastasis induced by PTC and point the way for the treatment of similar diseases in the future.

**Key Words:** Papillary thyroid cancer; Tyrosine kinase inhibitor; Neoadjuvant anlotinib therapy; Literature review; Case report

**Core Tip:** Cutaneous metastasis to the scalp is a site in patients which occurs after papillary thyroid cancers (PTC). Tyrosine kinase inhibitors represent a new approach to treat certain types of thyroid cancer. Here we report a case of scalp metastasis caused by PTC, in which neoadjuvant therapy of anlotinib before thyroidectomy was beneficial in reducing the thyroid and skull metastasis tumor sizes. Anlotinib maintenance regimen after thyroidectomy reduced the size of the metastatic skull tumor further, which successfully avoided the need for craniotomy.

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## INTRODUCTION

Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) are the two most common differentiated thyroid tumors (DTC)[1,2], with lymph nodes metastasis occurring frequently, but cutaneous metastasis to the scalp being a rare site. The average survival time for patients with thyroid carcinoma skin metastasis was about 19 mo from the end of the last century[1]. Most patients with thyroid cancer undergo surgery combined with subsequent radioactive iodine (RAI) therapy to clear any remaining tumor tissue and to prevent thyroid cancer recurrence[3]. RAI therapy is also given for more advanced cancers and/or cancers that have spread to lymph nodes or distant areas[4]. Apart from these regular treatment regimens, novel target therapies including a tyrosine kinase inhibitor (TKI) has become a new approach to treat certain types of thyroid cancer.

For example, sorafenib was approved by the United States Food and Drug Administration (FDA) in 2014 for the treatment of radioiodine-resistant DTC with metastasis[5]. Anlotinib is a new TKI that targets the vascular endothelial growth factor, fibroblast growth factor and platelet-derived growth factor receptors as well as c-kit[6]. Anlotinib was approved as third-line therapy for refractory advanced non-small-cell lung cancer in 2018, and as second-line treatment for advanced soft-tissue and clear cell sarcomas in 2019 in China[7]. In a preclinical study, anlotinib inhibited the cell viability of PTC, suppressed migration of thyroid cancer cells *in vitro* and also xenograft thyroid tumor growth in mice [8]. In a phase 2b study of medullary thyroid cancer patients treated with anlotinib, the median progression free survival (PFS) was found to be significantly prolonged (20.7 vs 11.1 mo)[9]. Another recent case of a patient with recurrent and metastatic radioactive iodine-refractory DTC (RAIR-DTC) treated with anlotinib showed a partial response after 2 cycles of anlotinib treatment and a PFS of 37 mo [10].

## CASE PRESENTATION

### Chief complaints

A 72-year-old woman presented to our hospital with a scalp mass on November 3, 2020.

### History of present illness

A scalp mass biopsy puncture indicated that thyroid cancer metastasis.

### History of past illness

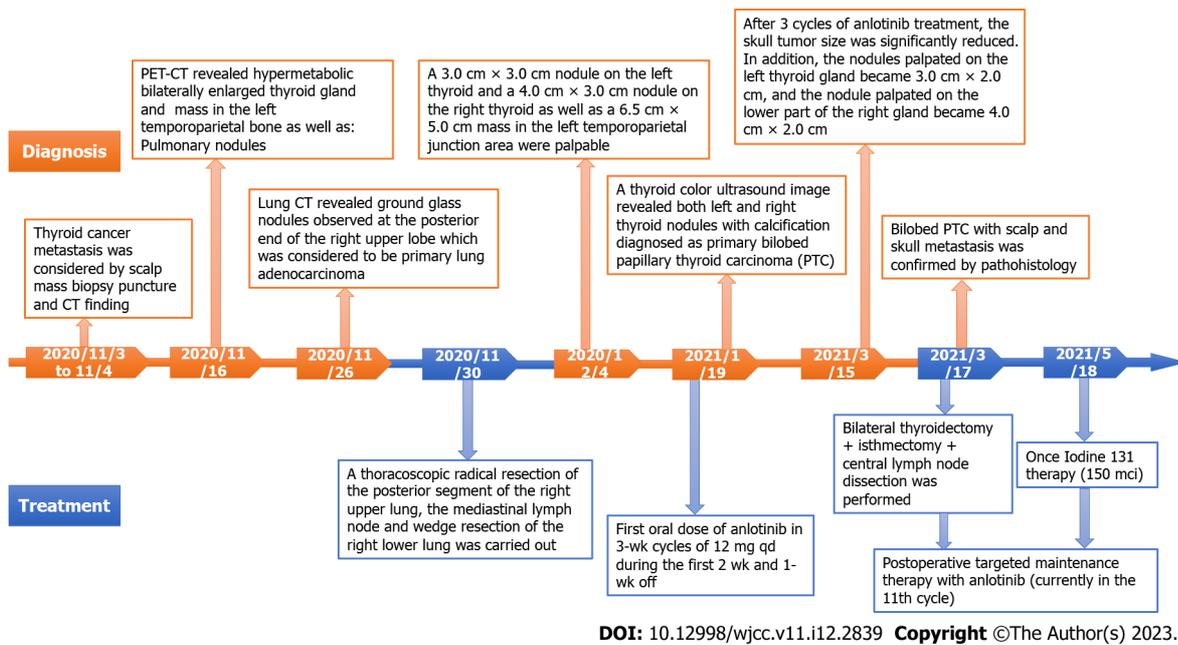
The patient had no previous history of any illnesses.

### Personal and family history

The patient had no previous personal and family history.

### Physical examination

On December 4, 2020, a 3.0 cm × 3.0 cm nodule was palpable on the left thyroid and a 4.0 cm × 3.0 cm nodule was palpable on the right thyroid. In addition, a 6.5 cm × 5.0 cm mass was palpable in the left temporoparietal junction region.



**Figure 1** A scheme of the diagnoses and treatments in chronological order. PTC: Papillary thyroid cancer; PET-CT: Positron emission tomography-computed tomography.

### Laboratory examinations

Immunohistochemical results: TTF-1 (+), CK7 (+), NapsinA (+), CDX-2 (-).

### Imaging examinations

A scheme of the diagnoses and treatments in chronological order is provided in [Figure 1](#). On November 16, 2020, a positron emission tomography-computed tomography (PET-CT) imaging diagnosis was conducted in which a hypermetabolic mass was revealed in the left parietal skull bone, indicating skin metastasis ([Figure 2A](#)), which was confirmed by a fine-needle aspiration biopsy diagnosis ([Figure 2B](#)). In addition, a bilaterally enlarged thyroid gland with increased metabolism was found ([Figure 2C](#)).

Lung CT was performed on November 26, 2020, which revealed ground glass nodules at the posterior end of the right upper lung lobe and in the dorsal portion of the right lower lung lobe. The ground glass nodules observed at the posterior end of the right upper lobe may correlate with the possibility of primary lung adenocarcinoma and oblique fissure. Both lungs exhibited scattered ground glass patches, likely due to chronic inflammation.

On January 19, 2021, A thyroid color ultrasound image revealed a left thyroid nodule with calcification (Chinese TI-RADS category 4) and a right thyroid nodule with calcification (Chinese TI-RADS category 3c)[11] ([Figure 3](#)).

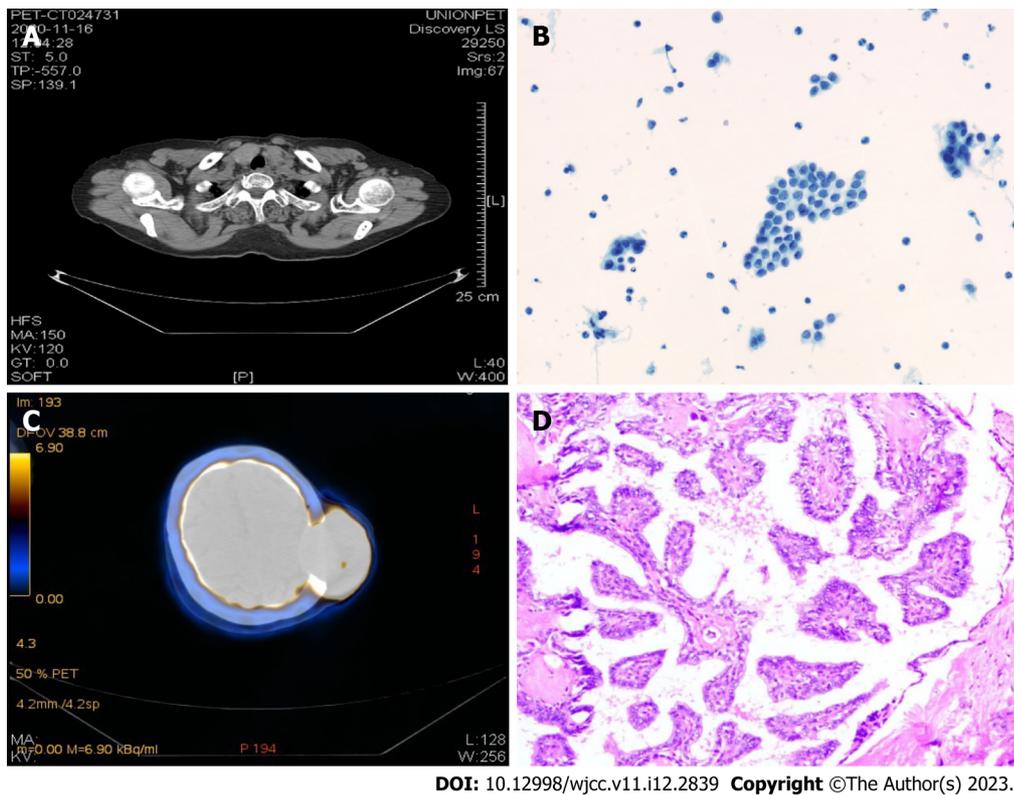
## FINAL DIAGNOSIS

According to the findings, bilobed PTC with scalp and skull metastasis was diagnosed based on histopathology data and PET-CT imaging. Next-generation sequencing (NGS) by an Illumina Novaseq 6000 system (Illumina, San Diego, CA, United States) revealed mutations in the BRAF, KRAS and IGF1R genes of the PTC. In addition, neck metastasis of the PTC and primary lung cancer were provisionally diagnosed.

## TREATMENT

On November 30, 2020, a thoracoscopic radical resection of the right upper lung cancer (resection of the posterior segment of the right upper lung + mediastinal lymph node sampling) plus wedge resection of the right lower lung were carried out. The operation went without complications and the postoperative recovery of the patient was good.

On January 19, 2021, the patient was given the first oral dose of anlotinib in 3-wk cycles of 12 mg qd during the first 2 wk and 1-wk off ([Figure 3B](#)). After 3 cycles of anlotinib treatment, the skull tumor size was significantly reduced. The nodule palpated on the left thyroid gland became 3.0 cm × 2.0 cm, and



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**Figure 2** Histological and computed tomography images of the skull tumor. A: positron emission tomography-computed tomography (PET-CT) imaging of the thyroid performed on initial diagnosis of the patient (November 16, 2020); B: Pathology of scalp mass biopsy (November 3, 2020). Scalp tumor histology similar to papillary thyroid carcinoma; papillary thyroid carcinoma metastasis was considered; C: PET-CT imaging of scalp metastasis (November 16, 2020). Note the hypermetabolic mass in the left temporoparietal bone, thinning of the corresponding temporoparietal bone due to compression, and local disappearance of the cerebral sulcus on the left side; D: Postoperative thyroid nodule pathology (paraffin) (March 18, 2021). Papillary thyroid carcinoma, classical type, interstitial fibrosis, no nerve infiltration or blood vessel invasion were observed. The tumor involved extra-glandular fibrofatty tissue.

the nodule palpated on the lower part of the right gland became 4.0 cm × 2.0 cm. In addition, preoperative color ultrasonography also showed that the thyroid tumor size was significantly reduced after neoadjuvant anlotinib therapy (Figure 3E).

A thyroidectomy was performed on March 17, 2021 with the left thyroid lobule and isthmus and the right thyroid lobule and lymph nodes in the central region successfully removed. The histopathology confirmed PTC (Figure 2D). Targeted maintenance therapy of anlotinib was administered after the operation in order to avoid craniotomy (Figure 3C).

## OUTCOME AND FOLLOW-UP

By postoperative day 2 (March 18 2021), the neck incision had healed and the patient recovered well. The intact parathyroid hormone concentration was 1.10 pmol/L and the electrolytic calcium concentration was 2.21 mmol/L.

Once iodine-131 therapy (dosage: 150 mci) was performed after the operation on May 18, 2021 and continued in combination with anlotinib (currently in the 11<sup>th</sup> cycle), a regimen which successfully avoided the need for craniotomy.

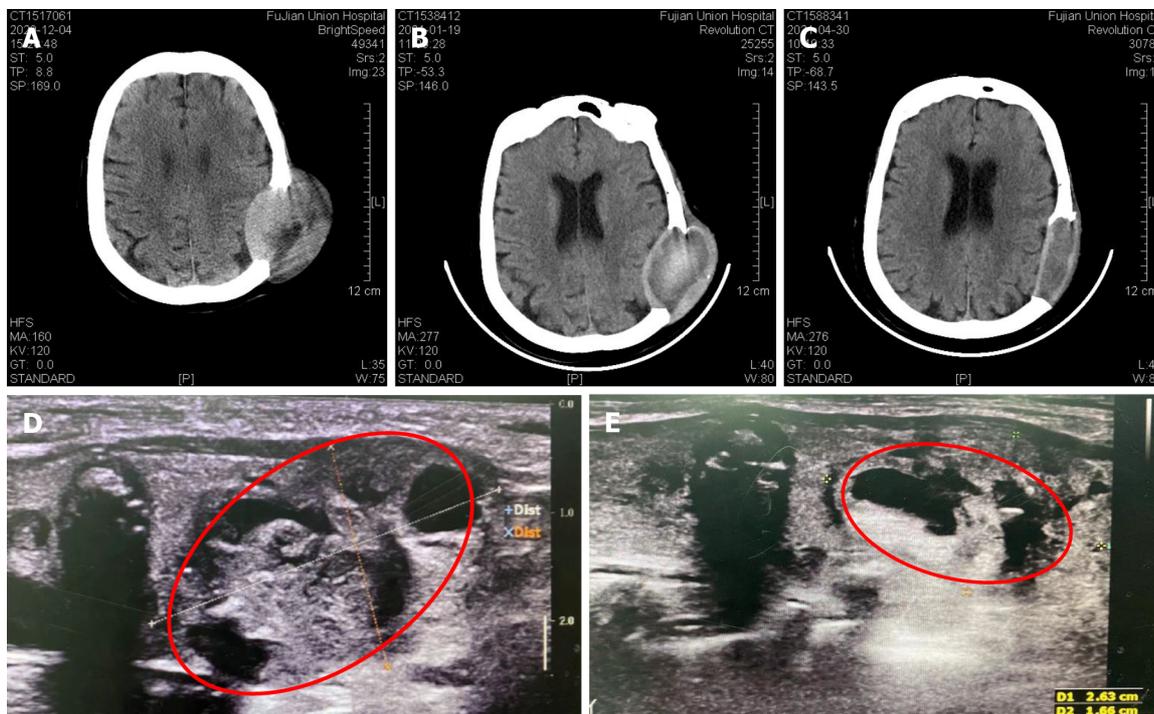
## DISCUSSION

The 4 main subtypes of thyroid carcinoma are papillary, follicular, medullary and anaplastic forms[12], with PTC being the most frequently occurring followed by FTC[13,14]. In this case report, the potential of anlotinib therapy to treat scalp metastasis induced by PTC was demonstrated. Scalp metastasis of thyroid cancer has been also described in other case reports[15-22] (Table 1). Most of the patients were females of advanced age with FTC and in the majority of the cases the skull metastasis had been diagnosed before thyroid cancer, as in the present case. Only 2 patients received post-operative TKI medication and the lung was the major organ of cancer lesions, which were supposed to be metastatic (Table 1). TKIs are small molecules which inhibit the activity of tyrosine kinases (Figure 4).

**Table 1** List of case reports about scalp metastasis of thyroid cancer published during the last decade

Gender	Age	Type	Time of diagnosis	Metastasis	Treatment	Ref.
Female	51	Follicular	Before thyroid cancer	Lung, bone	Surgery, I-131	[15]
Female	64	Papillary	After medical history of total thyroidectomy	Lung, liver	Excisional biopsy I-131	[16]
Female	37	Follicular	Before thyroid cancer	Lung, bone, cranium	Resection, I-131, post-operative TKI	[17]
Female	60	Follicular	Before thyroid cancer	No	Surgery	[18]
Female	70	Follicular	Before thyroid cancer	Lung	Surgery, I-131	[19]
Female	75	Follicular	1 year after thyroidectomy	Lung	Surgery, I-131	[20]
Male	65	Papillary	Before thyroid cancer	Vertebral and iliac lesions	Shave biopsy, I-131, post-operative sorafenib	[21]
Female	49	Follicular	4 years after thyroidectomy	No	Surgery, I-131	[22]

TKI: Tyrosine kinase inhibitor.



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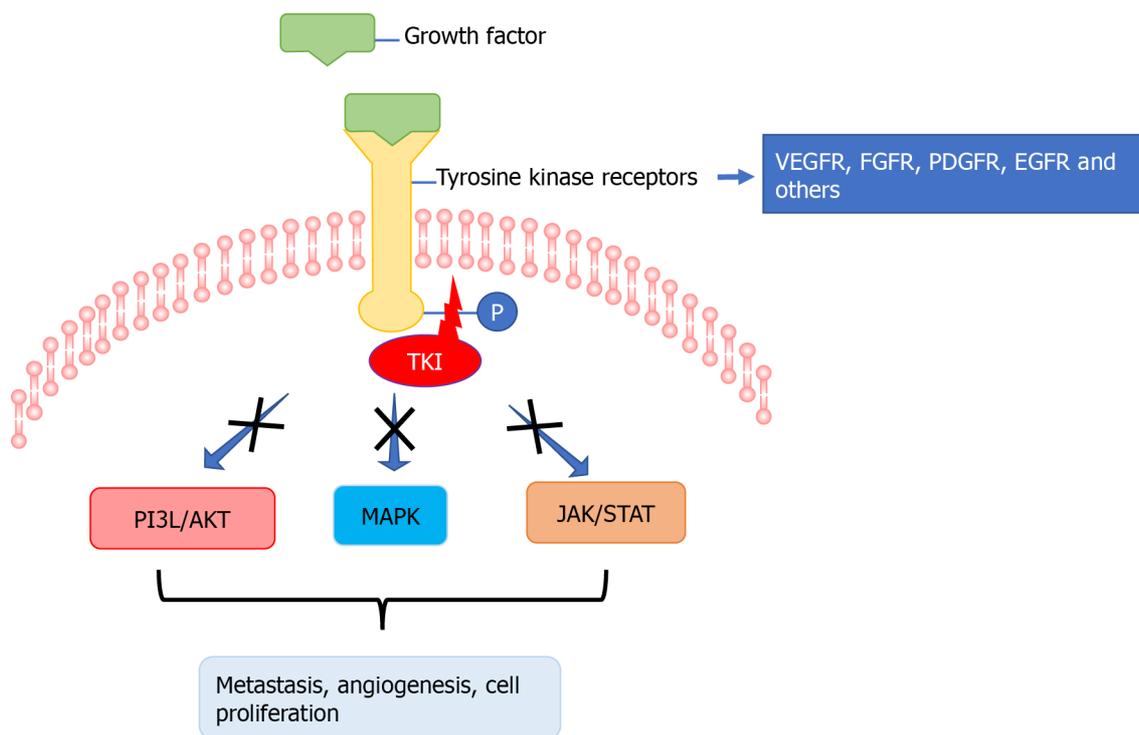
**Figure 3** Computed tomography image and color ultrasound of the skull throughout the treatment course and of the thyroid gland. A-C: Computed tomography images at admission (November 4, 2020; A), at the start of anlotinib treatment (January 19, 2021; B), and during maintenance medication (April 30, 2021; C); D: Color ultrasound images of a thyroid nodule with calcification (January 19, 2021); E: Preoperative color ultrasonography showed that the thyroid tumor size was significantly reduced after neoadjuvant anlotinib therapy (March 15, 2021).

TKI therapy is usually the final option for metastatic lesions, which are normally incurable by surgery and/or RAI therapy combined, but encouragingly a study involving 147 patients demonstrated that TKI treatment improved the prognosis of patients with distant metastasis and progressive disease[23]. A number of TKIs have been approved by the FDA to treat thyroid cancer, including vandetanib, cabozantinib, sorafenib and lenvatinib (Table 2). Vandetanib and cabozantinib were the first and second approved drugs for the therapy of advanced and progressive and/or symptomatic medullary thyroid cancer[24,25]. Sorafenib was approved for the treatment of <sup>131</sup>I-refractory DTC after the findings of the phase 3 DECISION clinical trial[26]. Lenvatinib is an anti-angiogenic TKI that has been approved for the treatment of advanced and progressive <sup>131</sup>I-refractory DTC[27]. A real-world study conducted in the United States demonstrated that treatment with first-line lenvatinib followed by subsequent second-line therapy delivered a clear clinical benefit[28]. A study carried out in Korea mainly focused on the adverse events of TKIs (lenvatinib and sorafenib) elicited in patients with DTC. Seventy-one cases (lenvatinib,  $n = 23$ ; sorafenib,  $n = 48$ ) were involved without new safety concerns being identified for either drug. Most AEs were managed with dose modification and medical therapy[29]. In former *in vitro*

**Table 2 Tyrosine kinase inhibitors for treatments of thyroid cancer**

Medication	Target	Indication	Ref.
Vandetanib	RET-tyrosine kinase, VEGFR and EGFR	Unresectable locally advanced or metastatic thyroid cancer	[24]
Cabozantinib	c-Met- tyrosine kinase, VEGFR 2, RET-tyrosine kinase, AXL	RAIR locally advanced or metastatic thyroid cancer after VEGFR-targeted therapy	[25]
Sorafenib	VEGFR 1-3, PDGFR and RAF and RET-kinases	Metastatic RAIR thyroid cancer	[26]
Lenvatinib	VEGFRs 1-3, FGFRs 1- 4, PDGFR- $\alpha$ , RET and KIT signaling	RAIR thyroid cancer	[27]

AXL: Tyrosine-protein kinase receptor UFO; FGFR: Fibroblast growth factor receptor; PDGFR: Platelet-derived growth factor receptor; RAIR: Radioactive iodine-refractory; VEGFR: Vascular endothelial growth factor receptor.



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**Figure 4 Scheme of tyrosine kinase inhibitor activity.** In order to activate signal transduction cascades, tyrosine kinase receptors must be phosphorylated by a tyrosine kinase in addition to binding with their specific ligands. Tyrosine kinase inhibitors block the activity of tyrosine kinases *via* different mechanisms. TKI: Tyrosine kinase inhibitor; P: Phosphate; PI3L/Akt: Phosphatidylinositol-3-kinase/Akt; MAPK: Mitogen-activated protein kinase; JAK/STAT: Janus kinase/signal transducer and activator of transcription.

experiments, anlotinib reduced the viability of PTC and anaplastic thyroid cancer cell lines, most likely due to aberrant spindle assembly, G2/M arrest and TP53 activation, while in a murine model anlotinib suppressed migration and growth of thyroid tumor xenografts[8]. Recently, a phase 2 trial of anlotinib in Chinese patients with radioiodine-refractory DTC showed promising results with a median PFS of 40.54 mo in the treatment group compared to 8.38 mo in the placebo group at a data cutoff date of January 2020[30].

Nevertheless, the present case report can be considered as a kind of pilot study. Besides conservative treatments, anlotinib has been used as neoadjuvant therapy, which significantly reduced the sizes of a metastatic skull tumor and of the primary PTC, while in combination with anlotinib maintenance medication a craniotomy was avoided.

NGS analysis of the PTC found mutations in the *BRAF*, *KRAS* and *IGF1R* genes, which did not match with the previously described undeferential thyroid cancer specific mutations of the *TERT* promoter, *RET* fusion and *TP53*[31]. On the other hand, *BRAF* mutations have been found to be key drivers of DTC, leading to the proposal of *BRAF*-directed therapies[32]. In line with the findings of the present study, a recent case report found that anlotinib was effective for the treatment of a RAIR-DTC patient with *TERT* promoter and *BRAF* mutations[10]. Another case report of a RAIR-DTC PTC patient with a *BRAF*<sup>V600E</sup> mutation noted that the patient developed tumor progression, with clinical symptoms that

worsened after dabrafenib-trametinib withdrawal[33]. In our case we will continue to monitor the outcome of anlotinib maintenance therapy.

A limitation of the present study was the lack of NGS and histopathology data about the lung lesions and the neck lymph nodes, which had been provisionally diagnosed as primary lung cancer and PTC metastasis into the neck.

## CONCLUSION

Neoadjuvant therapy of anlotinib before surgery was beneficial in reducing the thyroid tumor volume, but also that of the metastatic skull tumor. A craniotomy was thus avoided by using anlotinib maintenance therapy. Our findings point the way for the treatment of similar diseases in the future.

## FOOTNOTES

**Author contributions:** Zhang LY and Zhao WX contributed to the study design; Liang BY and Yan SY contributed to the data collection; Cai SJ, Wang B and Li MY contributed to the data analysis and interpretation; Zhang LY, Cai SJ and Yan SY wrote the draft; Wang B, Li MY and Zhao WX contributed to the revising/editing draft; all authors read and approved the final manuscript.

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