Letter to the Editor

Surgical resection following therapy with anlotinib in locally advanced papillary thyroid carcinoma: a case description

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Introduction

Anlotinib is a newly small molecule receptor multitarget tyrosine kinase inhibitor (mTKI) targeting vascular endothelial growth factor receptors (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), and c-kit, which can simultaneously inhibit tumor angiogenesis and cell proliferation (1). There is poor or low activity and expression of most carcinogenic receptor tyrosine kinases (RTKs) in normal tissues and cells, while the activity and expression of RTKs is excessive or the level of carcinogenic RTK levels is up-regulated in many malignant cells (2,3). Vascular endothelial growth factor (VEGF) and VEGFR are often overexpressed and activated in thyroid cancer cells, and angiogenesis exert carcinogenic effect in the development and progression of thyroid cancer (TC) (4,5). Anlotinib can inhibit VEGFR2 with high selectivity (IC50 <1 nmol/L) when combined with the hydrophobic region of the adenosine triphosphate (ATP) binding domain of VEGFR2 Tyrosine kinase, suppressed the growth of microvessels *in vitro* and reduce the density of vessels *in vivo* (6). In addition, the antiangiogenic activity of anlotinib is significant, which is superior to several common drugs (such as Sorafenib) (7).

Preoperative targeted therapy is one of the accepted protocols for the treatment of several human tumors to reduce the tumor load allowing for subsequent surgical treatment. However, it is an unconventional event in the management of thyroid cancer. Here, we report a patient with locally advanced unresectable follicular thyroid carcinoma (FTC) who showed a significant reduction in tumor size after targeted therapy with anlotinib, allowing subsequent surgical resection and radioactive iodine therapy (RAIT).

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institution and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

The case report involved a 52-year-old man with hyperthyroidism (treated with ^{131}I previously) and diabetes for 2 years (taking oral hypoglycemic drug). He visited a nearby clinic with complaints of left clavicle discomfort for a year, and he underwent diagnostic fine needle aspiration (FNA) of left thyroid nodule in nearby clinic, being diagnosed with FT-UMP (follicular tumor of uncertain malignant potential). Then he was admitted to the surgical department of our hospital for another FNA of left thyroid nodule revealing the possibility of papillary thyroid carcinoma (PTC). A contrast-enhanced computed tomography (CT) scan of the

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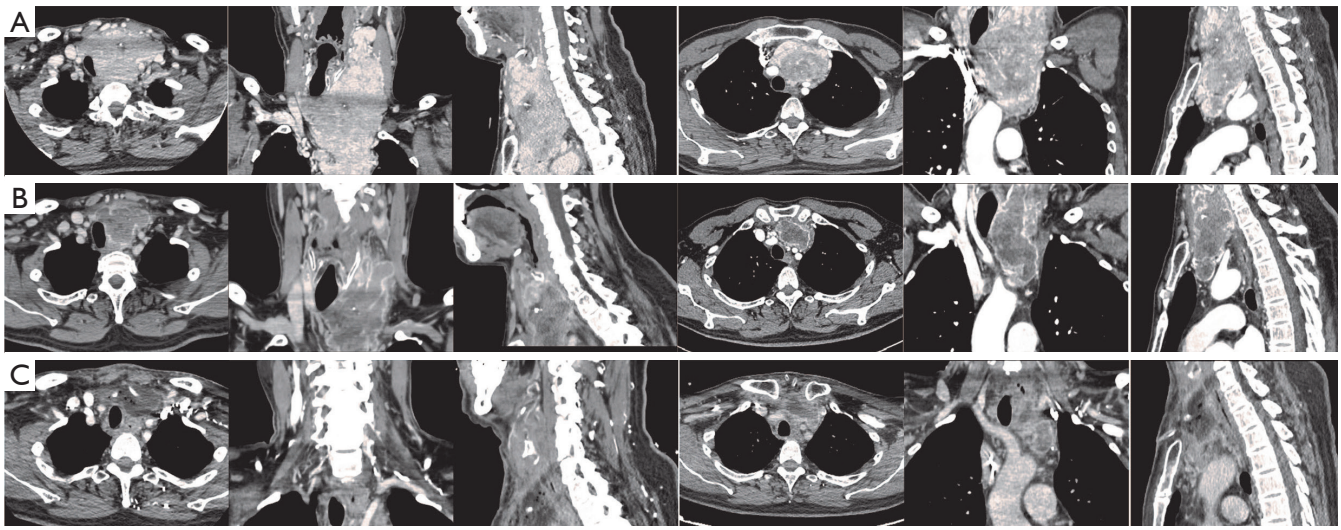

Figure 1 Contrast-enhanced CT images at different times. (A) Initial visit; (B) after 6 cycles of therapy with anlotinib; (C) 6 days after operation. CT, computed tomography.

neck and thorax revealed a lesion of 12.1×9.5 cm (in the largest cross section) starting on left neck and spreading down the mediastinum with invasion into the trachea and internal jugular vein, forming a tumor embolus in the left internal jugular vein, and bilateral pulmonary multiple suspicious nodules (maximum diameter 8 mm) (*Figure 1A*). The preoperative conference suggested that it was difficult to resect the tumor completely and safely due to the size of tumor and severe involvement of the surrounding structures. Anlotinib, a new multikinase inhibitor (MKI), was initiated considering the significant antiangiogenic ability, good tolerance and the patient's economic conditions. After 6 cycles of targeted therapy with anlotinib (12 mg oral daily, two weeks on/one week off), the tumor had shrunk to 5.0×4.3 cm which could be assessed as a partial response according RECIST evaluation (8), and multiple suspicious nodules in lungs were reduced and shrunk (maximum diameter 6 mm) (*Figure 1B*). The thyroglobulin (Tg) on centration also dropped from over 500 to 339.8 ng/mL. In the course of preoperative targeted therapy with anlotinib, there were no side effects other than well-controlled hypertension (diastolic pressure, 90–110 mmHg) and unstable blood glucose level (8.0–13.0 mmol/L). Initially the neck and chest (mediastinum) surgery were planned, but after consultation and evaluation by several surgeons, the neck surgery was finally performed in consideration of the patient's physical condition and surgical risk. Tg levels were reviewed before surgery but showed another rise (≥500 ng/mL). In the operation, multiple solid masses in the left lobe and isthmus of thyroid gland were integrated into the group involving muscle invasion. The lower pole of the tumor could not be completely removed because left subclavian vein was severely adherent to the tumor. The left parathyroid gland and recurrent laryngeal nerve were resected due to severe tumor invasion. The surgical product sent to histopathological department demonstrated a 10 cm FTC on the left lobe and isthmus and 1.5 cm on the right lobe. The postoperative CT displayed the reduction of mediastinal lesion and the thyroid gland was completely removed (*Figure 1C*). The postoperative course was critical because of severe surgical trauma, with need for ventilatory support, and the patient was transferred to ICU for further symptomatic treatment for 4 days to prevent any potentially life-threatening condition. One week later, the patient's condition was stable and he was discharged home. There were no other postoperative complications except for hoarseness.

Since there was a large amount of residual tumor tissue, the patient received postoperative therapy of anlotinib and ^{131}I. The patient received 5.50 GBq (150 mCi) of ^{131}I therapy 3 months after operation. 1 month after thyroid-stimulating hormone (TSH) withdrawal, his serum TSH was 78.19 mIU/L, and the Tg on centration before ^{131}I treatment was 1,784.00 ng/mL (reference range, 1.4–78 ng/mL) with negative thyroglobulin antibodies (TgAb). The chest CT showed a nodule (5 mm) in the right lung and soft tissue masses in the left neck and upper mediastinum. The post-therapy whole-body scan (Rx-WBS) was performed 48 hours later showing uptake at the thyroid

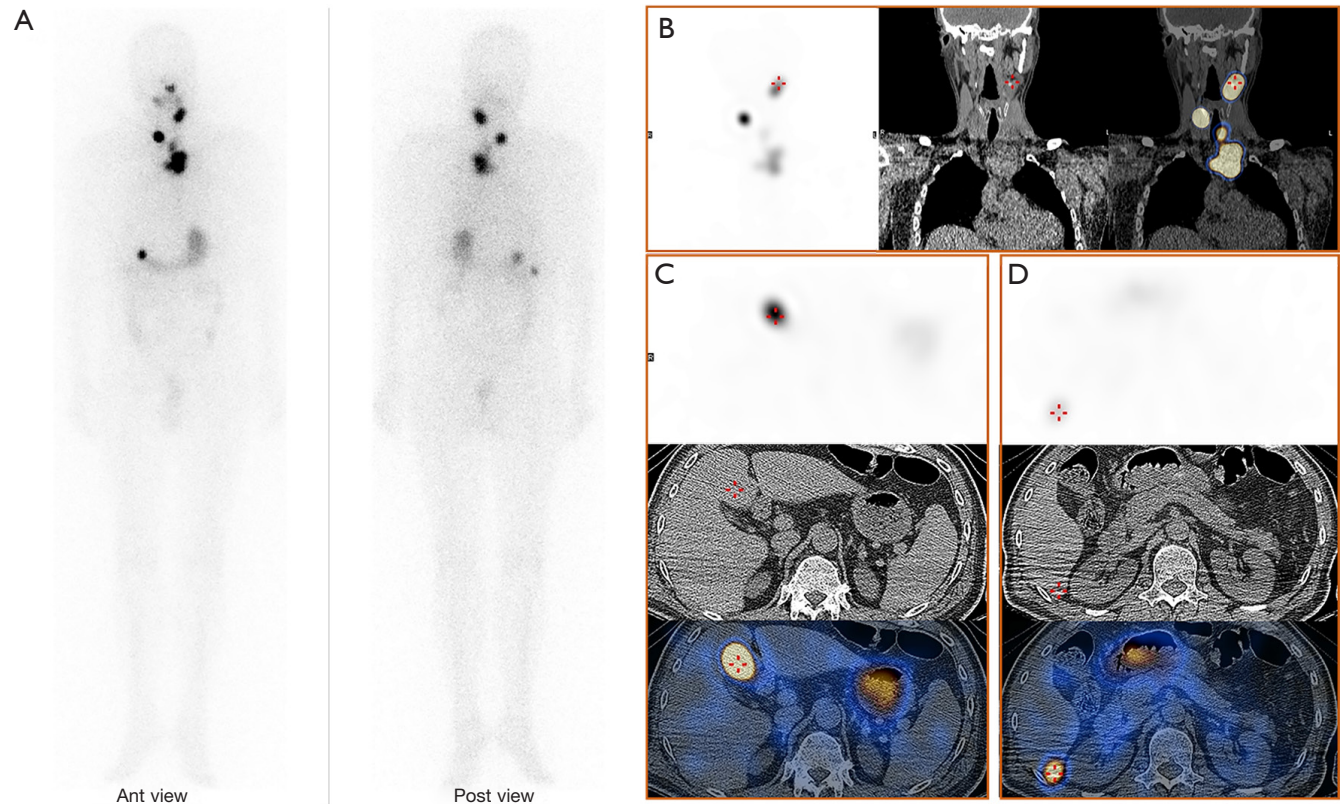

Figure 2 SPECT/CT images after the first RAIT. (A) Planar images of Rx-WBS; (B) fusion images of SPECT/CT in the neck and upper mediastinum; (C,D) fusion images of SPECT/CT images in the right lateral lobe of the liver. SPECT/CT, single-photon emission tomography/computed tomography; RAIT, radioactive iodine therapy; Rx-WBS, post-therapy whole body scan.

bed, lesions in the left neck and upper mediastinum and 2 foci in the right lobe of liver (*Figure 2A*). CT appearance of hepatic lesions was slightly low-density image with a less distinct margin. The scanning results confirmed FTC in the left neck and upper mediastinum (6.0×5.0×2.5 cm) with left cervical lymph node metastasis (2.0*1.0 cm) and possible liver metastasis finally (*Figure 2B-2D*). There was no uptake in the right pulmonary nodules. Four months after RAIT, the contrast-enhanced CT showed smaller lesion of mediastinum and reduction and shrinkage of nodules in lungs (2–3 mm) (*Figure 3*). The patient's serum stimulating Tg level decreased from 1,784.00 to 290.40 ng/mL during 6 months of follow-up, and the ultrasound examination showed that the lesions and lymph node of the left neck area were significantly smaller than before. The chest CT showed a nodule (3 mm) in the right lung and smaller soft tissue masses in the left neck and upper mediastinum. Thus, a second ^{131}I treatment was performed to evaluate the effect on metastatic thyroid cancer and for further therapy. The Rx-WBS demonstrated multifocal radioiodine accumulation of neck, chest, and the right abdomen, and the uptake of all lesions was reduced compared with the previous Rx-WBS (*Figure 4A*). Single-photon emission computed tomography/computed tomography (SPECT/CT) fusion images showed that abnormal uptake of neck and chest is located in the left neck and upper mediastinum (2.8*3.0*1.5 cm), left cervical lymph node (13*5 mm) (*Figure 4B-4D*). The location of liver uptake was the same as before, but there was no abnormal density in CT. The nodule in right lung was still no uptake. Lung nodules were not biopsied due to their small size, and we will continue to monitor them with suspicion. The patient is being followed up, and alive more than 12 months after surgery. The time line of treatment, the size of tumor and serum index of patients are shown in *Figure 5*, *Figure 6* and *Table 1*.

Discussion

Studies have shown that anlotinib can exert significant efficacy and relatively acceptable toxicity in some advanced

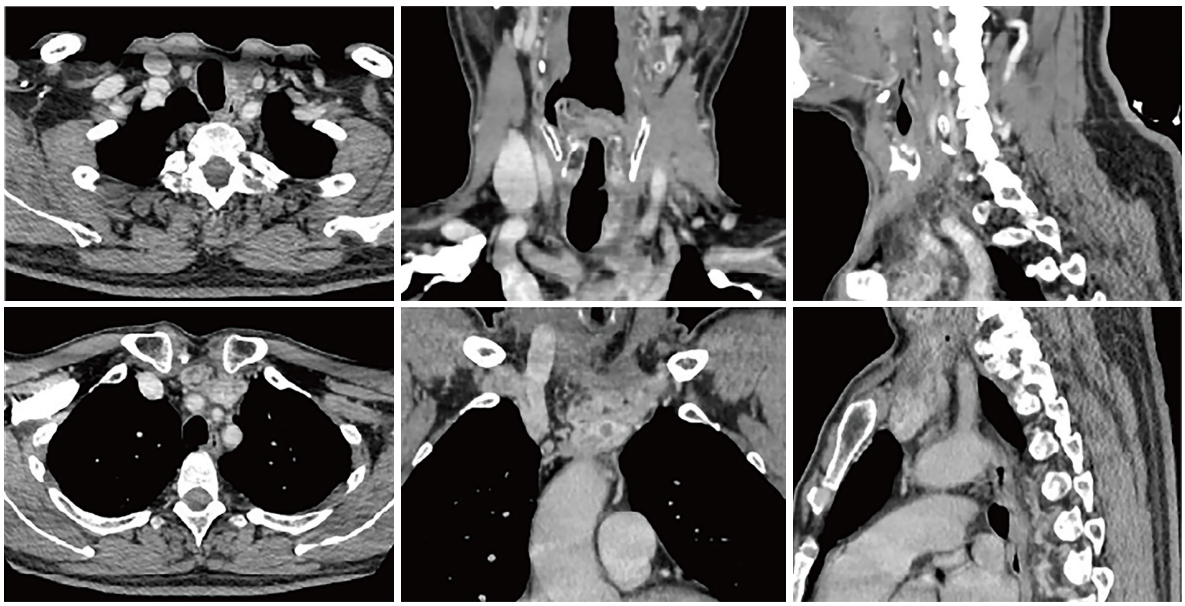

Figure 3 Contrast-enhanced CT images at 4 months after the first RAIT. CT, computed tomography; RAIT, radioactive iodine therapy.

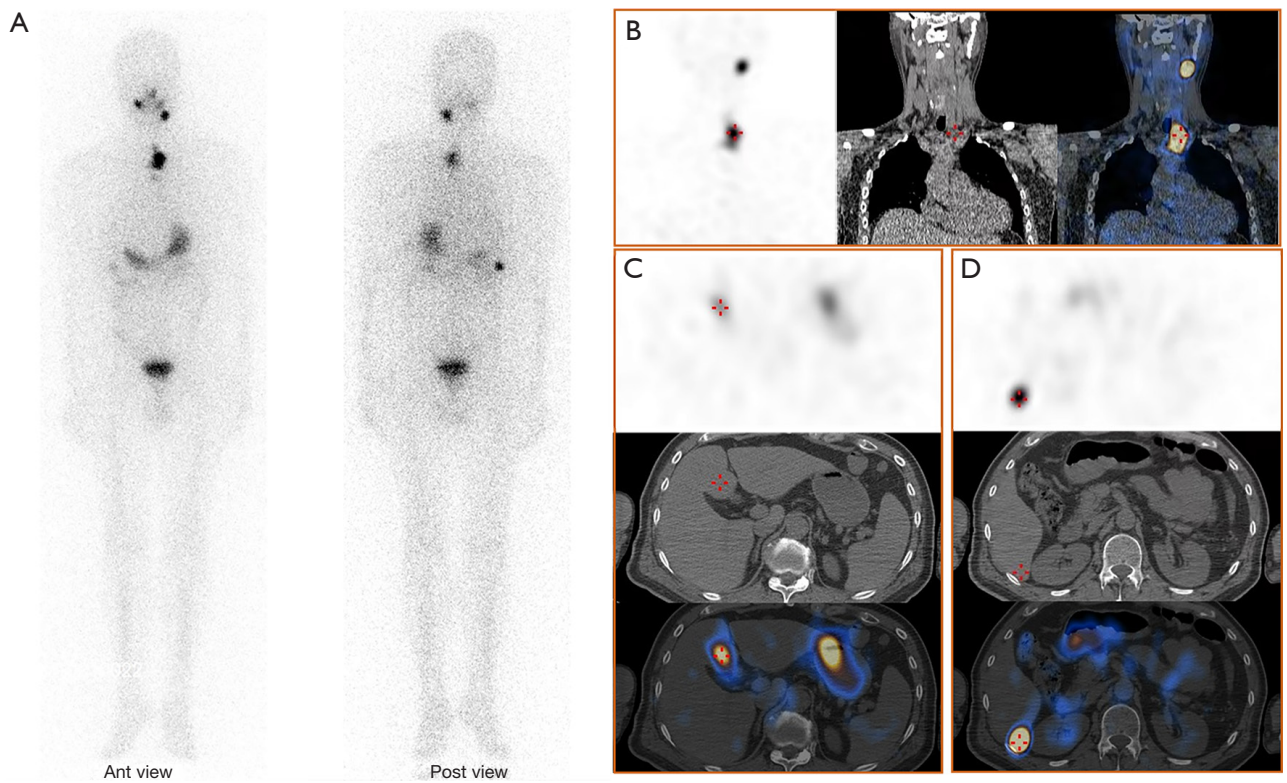

Figure 4 SPECT/CT images after the second RAIT. (A) Planar images of Rx-WBS; (B) fusion images of SPECT/CT in the left neck and upper mediastinum; (C,D) fusion images of SPECT/CT in the right lateral lobe of the liver. SPECT/CT, single-photon emission tomography/computed tomography; RAIT, radioactive iodine therapy; Rx-WBS, post-therapy whole body scan.

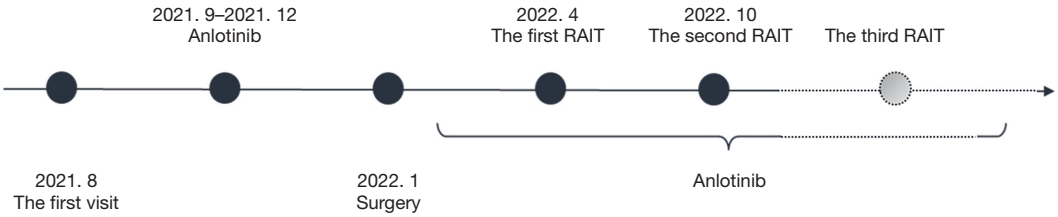

Figure 5 Timeline of diagnosis and treatment. RAIT, radioactive iodine therapy.

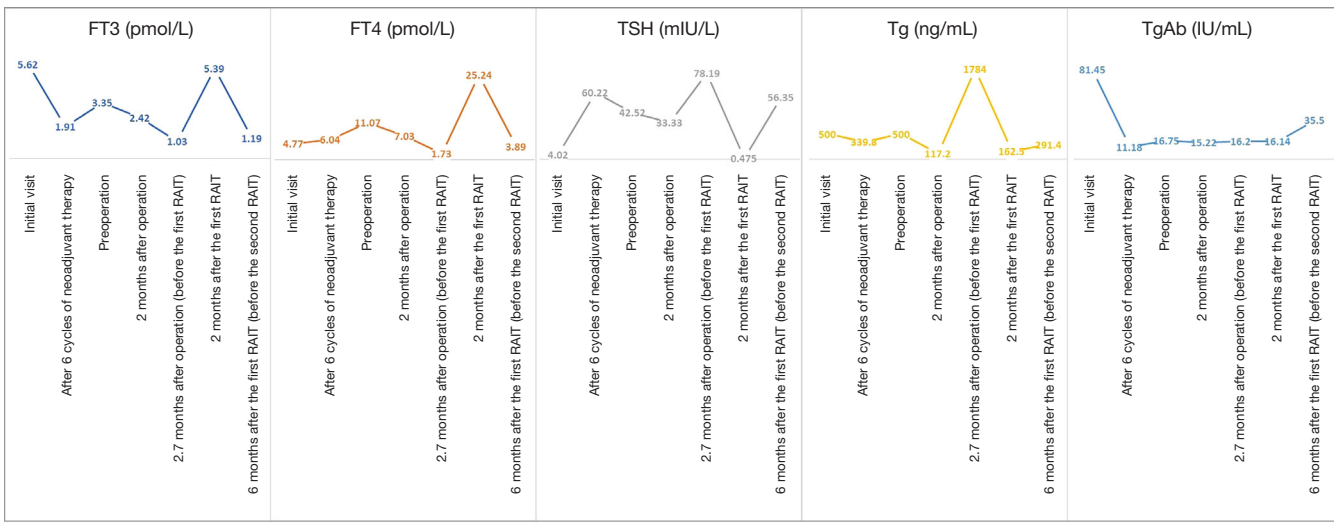

Figure 6 The changes of serum index (as the limit values of different institutions are different, "500" in Tg means ≥500). RAIT, radioactive iodine therapy.

Table 1 The size of tumor at different time

Timeline	The largest cross section/ volumes (cm)
Initial visit	12.1×9.5
2 months after target therapy	5.0×4.3
After 6 cycles of target therapy	5.0×4.3
Pre-operation	5.1×4.6
The first RAIT	6.0×5.0×2.5
The second RAIT	2.8×3.0×1.5

RAIT, radioactive iodine therapy.

malignancies, such as non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), soft tissue sarcoma (STS) and metastatic renal cell carcinoma (mRCC). A randomized controlled, double-blind, multicenter, phase III trial (ALTER-0303) demonstrated a favorable efficacy and safety of anlotinib in patients with advanced NSCLC who had progressed after at least two prior treatments (9). Compared with that of the placebo group, the anlotinib group improved objective response rate (ORR) and disease control rate (DCR) (ORR 9.2% *vs.* 0.7%, P<0.0001; DCR 81.0% *vs.* 37.1%, P<0.0001) and prolonged median progression free survival (PFS) and overall survival (OS) (PFS 5.37 *vs.* 1.40 months, P<0.0001; OS 9.63 *vs.* 6.30 months, P<0.0001) significantly. ALTER-1202 was a Phase II clinical study of anlotinib for Third Line and Above Treatment of SCLC which also showed the longer PFS and OS than the placebo group (10). Anlotinib also demonstrated better clinical efficacy in STS. Specifically, alveolar soft part sarcoma (ASPS) showed an excellent progression-free rate at week 12 (76.92%). A multicenter, single-arm, phase II study demonstrated that the ORR and DCR in the anlotinib group were significantly improved (ORR 10.1% *vs.* 1.3%, P=0.0145; DCR 55.7% *vs.* 22.7%, P<0.0001) and the median PFS relative to the

control was prolonged (6.27 *vs.* 1.47 months, P<0.0001) (11). In addition, anlotinib showed tolerable toxicity and good clinical efficacy in patients with mRCC who failed sorafenib or sunitinib treatment.

Previous studies showed promising antitumor efficacy of anlotinib in radioiodine-refractory differentiated thyroid cancer (DTC) and medullary thyroid cancer (MTC) (12,13). There are few studies involving preoperative targeted therapy of anlotinib for DTC but a Single-arm Phase II Clinical Trial which evaluated the efficacy and safety of anotinib preoperative treatment of locally advanced thyroid cancer according to the operation rate and adverse events of 13 patients after an average of 3.5 cycles of anlotinib treatment by Huang *et al.* recently. Antitumor activity of anlotinib in preoperative treatment of locally advanced TC was demonstrated, and most patients achieved R0/1 resection (14).

The vast majority of DTC, with excellent prognosis after clinical intervention (surgery and/or RAIT), present as locoregional tumors with rarely subsequent surgical morbidity and mortality. Occasionally when R0/R1 resection could not be achieved at initial diagnosis because the primary tumor is too large and/or has invaded critical structures, using targeted drugs to reduce tumor load before surgery would be an option.

Considering the potential antineoplastic activity and rapid response in several kinds of malignancies, especially the improvement of PFS, we chose anlotinib. Of course, economic factors cannot be ignored: the cost of anlotinib is relatively low, and it is also more available in China. The preoperative therapy resulted in partial response of cervical and thoracic thyroid cancer and R2 resection. Combined with ^{131}I after operation also achieved good therapeutic effect. In terms of side effects, we observed hypertension and blood glucose fluctuation. In the previous two ^{131}I treatments, residual thyroid cancer and metastatic lesions had good iodine uptake capacity. We evaluated that the patient can benefit from ^{131}I treatment and made an appointment for the follow-up ^{131}I treatment.

In our study, the treatment with anlotinib could make an inoperable tumor operable and improve the prognosis significantly with combination of ^{131}I. Although a series of clinical trials have confirmed the good survival benefits of anlotinib in the treatment of many kinds of solid tumours. Preoperative targeted treatment not specified in the current DTC guidelines. So, large-scale clinical trials are still needed to elucidate long-term efficacy and adverse effects and to quickly identify biomarkers that predict efficacy and prognosis, so as to identify those who will benefit best from anlotinib. It is believed that the clinical application of anlotinib will bring more benefits to patients with locally advanced DTC in the near future.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1334/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institution and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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