Preoperative neoadjuvant targeted therapy for inoperable differentiated thyroid cancer: a case report

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Case report

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Abstract

**Background:** The majority of differentiated thyroid cancer (DTC) has good prognosis after a careful standardized therapy according to the current guidelines. However, approximately 13% to 15% of DTC shows surprisingly aggressive behavior and invades the surrounding structures, and then a few is very difficult to remove. In that specific context, preoperative neoadjuvant targeted therapy may improve the clinical stage and create an opportunity for operation.

**Case presentation:** We reported a case of 64-year-old woman with locally advanced papillary thyroid cancer (PTC) who presented with dysphagia due to seemingly unresectable tumor, which severely invaded the left esophagus at the junction of neck and thorax, difficult to undergo a safe and complete removal. With an approval of institution ethics committee, this patient was treated with neoadjuvant therapy (apatinib 500mg orally qd).

Six weeks later, the tumor dramatically shrunk from 56*37mm to 29*26mm with well-controlled mild hypertension. After 10 days interval of apatinib withdrawal, complete tumor excision was accomplished without esophagus fistula. Postoperative inhibition and radioiodine 131I ablation were performed. At one-year follow-up evaluation, no tumor recurrence or metastasis was observed.

**Conclusion:** Preoperative short-termed targeted treatment for locally advanced inoperable DTC may become a promising neoadjuvant therapy, which can reduce the tumor size and decrease stage, thus being convenient for complete and safe removal.

**Background**

It is well known that thyroid cancer (TC) is the most common endocrine malignancy, and TC has been discovered to cause 41000 deaths worldwide in 2018 [1]. Differentiated thyroid cancer (DTC) refers to neoplasms derived from the thyroid follicular epithelial cell, and consists of papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and Hurthle cell thyroid cancer (HCTC) [2]. DTC comprised the vast majority (> 90%) of all TC [3], and generally carries good prognoses after a standard surgery with endocrine inhibition, sometimes also with radioactive iodine (RAI) therapy. Nevertheless, approximately 13%~15% of DTC cases could show surprisingly aggressive behavior and involve the surrounding structures such as recurrent laryngeal nerve (RLN), trachea, esophagus, larynx, pharynx, or major cervical vessels, which complicates the surgical treatment and dramatically increases postoperative complication and mortality, or even the tumor progresses to unresectable disease [4].

In fact, few guidelines dedicated to the optimal approach of these locally advanced TC [5]. Several kinds of methods can be tried, such as external beam radiation therapy (EBRT), systemic chemotherapy (ChT), molecule-targeted treatment, or even radioactive 125I seed implantation, chemo-embolization, thermal (radiofrequency or cryo-) ablation, ethanol ablation, but complete and adequate surgery for TC represents the main stay of the multimodal treatment approach and the most significant determinant of outcome [3]. Nevertheless, surgical management of advanced TC is complex and challenging, and in some cases,
it is difficult or impossible to perform an effective surgery. In that specific context, how can we improve the clinical stage and create an opportunity for operation? Similar to the breast conserving surgery or anus-preserving operation combined with pre-operative chemotherapy for the treatment of middle-advanced cancer, the neoadjuvant therapy would be worthwhile to try in DTC. Herein, we reported a case of locally advanced inoperable DTC patient who underwent a complete safe removal after receiving preoperative short-term apatinib targeted treatment, with little drug-related side effect and almost no postoperative complication.

**Case Presentation**

A 64-year-old woman was diagnosed as PTC with huge mass in left neck for 6 months, the patient felt dysphagia. The cytopathology indicated the tumor might be a malignancy in the local hospital. It is difficult to undergo totally surgical resection for severe tumor invasion of the esophagus.

The patient complained that the dysphagia symptom had gradually become worse within 6 months and she could only feed on fluid. She had no history of high blood pressure, diabetes, hyperthyroidism, autoimmune diseases or family illness. After physical examination, we found a large hard and immobile mass located in the left neck (with 7*6 cm in size) and no palpable lymphadenopathy. The hormones levels of thyroid function were normal except for a significantly increase of thyroglobulin (Tg) (1364.00 ng/ml, reference range: 3.50–77.00 ng/mL).

A repeat ultrasound inspection revealed a 36*39*73 mm hypoechoic mass with irregular modality, ill-defined border, heterogeneous internal echoes and abundant color flow signal. In addition, the opposite lobe existed several hypoechoic and cystic mixed echogenic areas, one of which was 13*8 mm in size with a distinct border and little color flow signal. Fortunately, there was no enlarged cervical or supraclavicular lymphadenopathy. Ultrasound-guided core biopsy in the left lobe of thyroid gland was performed and the pathology indicated PTC (Fig. 1).

A contrast-enhanced computed tomography (CT) scan of the neck revealed a 56*37 mm giant irregular mass in the left lobe of the thyroid gland, which involved adjacent structures and compressed the trachea and esophagus (Fig. 2a). The whole mass wrapped and compressed the esophagus, causing significantly esophageal stenosis and resulting in dysphagia. Magnetic resonance imaging (MRI) revealed similar results, and further confirmed the boundary between the tumor and trachea, also the esophageal compression and invasion (Fig. 2b). Esophagogastroduodenoscopy presented the stenosis of upper esophagus with no passing of the nasal gastroscope (Fig. 2c). As esophagram showed, the esophagus mucosa was less smooth locally, and the left esophageal wall was likely destroyed. So, it can be concluded that a significant compression and wall invasion of the upper esophagus existed but with no cervical lymphadenopathy.

Based on the discussion of the multi-disciplinary team, we estimated it was difficult to resect the tumor completely and safely due to the severe involving surrounding structures of trachea and esophagus. It might become a palliative operation if surgical treatment was given as the primary choice, and the risk of
esophageal fistula could also be high. Considering the potential antineoplastic activity of apatinib in several kinds of malignancies, our team proposed off-label preoperative targeted therapy for this specific case. Of course, economic factor cannot be ignored, the cost of apatinib was only one-fifth to one-half compared to sorafenib, and apatinib is also more available than sorafenib in China. Treatment was started with apatinib 500 mg orally once per day on February 14, 2019. Luckily, the adverse drug reaction occurred for only mild hypertension. One month after the therapy, the patient was benefited from the favorable clinical tolerability and safety, and an interval CT scan indicated tumor shrinkage as 36*25 mm in size and reduction of pressure degree on esophagus significantly (Fig. 3a). At the same time, serum Tg level decreased from 1364.00 to 861.20 ng/mL. These surprising findings seemed to be a good sign for disease remission.

After continuous administration of apatinib for six weeks, the patient felt remission of dysphagia. We reappraised the illness by a contrast-CT scan on April 1st, 2019, the result showed the size of tumor was 29*26 mm, a marked reduction (Fig. 3b). In this circumstance, we believed surgery could be less traumatic, complications could be more manageable and the esophagus could be preserved. Then, the total thyroidectomy, left central lymph node dissection and the muscular layer resection of the esophagus were smoothly completed. It is worth mentioning that the tumor had seriously invaded the left recurrent laryngeal nerve. Besides, no invasion or adhesion to the trachea was discovered. Postoperative pathology and immunohistochemistry revealed a PTC diagnosis with capsular invasion comprising CK19(+), MC(+), Galectin-3(+), TPO(-),TG(weak+),TTF-1(+), Ki-67(5–10%), PAX8(+) at the left lobe of the thyroid, and nodular goiter in the right lobe. In total, 1/2 lymph nodes were metastatic. Final TNM staging was pT4aN1aM0, stage II. It is necessary to emphasize that concurrent BRAF gene and TERT promoter mutations were found by genetic analysis in tumoral tissue, which indicated aggressive behavior of this PTC. We paid close attention to the recovery of the esophagus and found no esophageal fistula.

The level of Tg fell back to 4.80 ng/mL with anti-Tg antibodies (-) during the first month of follow-up. The level of TSH was adjusted to < 0.1 mU/L by levothyroxine dose to reduce the risk of disease recurrence. Six months later, neck ultrasonography found no residual TC or normal thyroid tissue, chest CT scan and whole-body bone scan (Fig. 4) undiscovered pulmonary or bone metastasis, while whole-body RAI scan (Fig. 5) indicates focal $^{131}$I uptake of the cervical thyroid bed. Then the patient received RAI remnant ablation with the administered activity of 100 mCi. One year after the surgery, the Tg level was 0.81 ng/ml and TSH was 0.02 mU/L. Besides, ultrasonography again was not abnormal. In the future, long-term follow-up to evaluate postoperative disease status is still necessary.

**Discussion And Conclusions**

Locally advanced TC generally refers to gross extrathyroidal extension (gETE) of primary tumor who passes the thyroid capsule and infiltrates the surrounding tissues. According to the 8th edition AJCC Cancer Staging Manual, gETE invasion into subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size is defined as T4a category, and the presence of gETE invading the prevertebral fascia, encasing carotid artery or mediastinal vessels is T4b [6]. Extensive gETE
portends an increased incidence of local recurrence, regional and distant metastasis [3]. Though management is controversial, it is well known that the most significant approach is to remove the neoplasm en bloc for local control and disease-free survival. However, the balance between radical surgery and functional preservation of the anatomical structures involved was required to be taken into account [7]. There is no doubt, surgical therapy of this locally advanced DTC is challenging and the resection scope remains controversial for lack of high-level evidence.

Research shows that free margins (R0) have better local control [8] compared with close or positive microscopic margins (R1), while incomplete resection has been associated with increased mortality [5, 9]. Besides, lower local control was observed in recurrent tumor versus initial tumor, and the contribution of postoperative adjuvant radiation therapy is limited [8]. In conclusion, attaining an R0/R1 resection by comprehensive operative clearance is critical and bound up with superior outcomes in T4 disease. Back to this case, demolitive surgery with reconstruction of the esophagus not only considerably aggravated the notable surgical trauma and postoperative complications, but also significantly decreased the patients' quality of life. Above all, the patient's acceptance to undergo such procedures seemed vacillating.

In this particular case, which methods can we try to reduce the tumor volume for improved resection margins and narrow the scope of surgery on the basis of R0/R1 resection? Neoadjuvant therapy for thyroid cancer still has not had an established role and not be mentioned in the 2015 ATA guideline [3]. Historically, only a few similar cases were found on review of the literature. Besic et al presented that preoperative ChT decreased the tumor size by > 50% in 45% patients (13/29) of FTC or HCTC, and in 44% (7/16) of locally advanced PTC [10, 11]. A case published in 1998 reported that preoperative $^{131}$I treatment is beneficial for inoperable TC [12]. Besides, one locally unresectable patient underwent a total thyroidectomy after neo-adjuvant EBRT [13]. Nonetheless, the large number of studies focused on targeted therapies, especially tyrosine kinase inhibitors (TKIs). For instance, surgical clearance was achieved in patients with locally advanced DTC after 14 months treatment of sorafenib and lenvatinib [14], or after 13 months of sorafenib monotherapy [15], or after 22 weeks of lenvatinib monotherapy [16]; the usage of lenvatinib for better local control of poorly DTC during waiting period for operation because of patient comorbidities [17]; a similar situation come up in medullary thyroid cancer (MTC) with sunitinib [18], or even in anaplastic thyroid cancer (ATC) with dabrafenib plus trametinib [19]. Nowadays, vandetanib and cabozantinib are approved by FDA for patients with progressive, metastatic, or unresectable MTC, while sorafenib and lenvatinib are for DTC patients with RAI-refractory. All these findings revealed that neoadjuvant therapy could potentially reduce the extent of invasion and risks of residual disease after surgical resection. In certain cases, it might be a valuable option when treatment is limited [20].

Pathological angiogenesis is an important characteristic and essential for tumor growth, invasion and metastasis, especially for solid tumor [21]. Vascular endothelial growth factor (VEGF) is a crucial and positive regulator in physiological processes. VEGFR-2, mainly expressing on endothelial cells, is the key signaling receptor of the pathway for mediating the mitogenic, angiogenic and permeability-enhancing
effects of VEGF. Thus, the therapy of targeting VEGF or VEGFR is mainly to focus on anti-angiogenesis. Apatinib, also known as Aitan (brand name in China) and developed independently by Shanghai Hengrui Pharmaceutical Co., Ltd (Shanghai, China) [22], is a typical representative of anti-angiogenesis agents for antineoplastic functions, which could induce apoptosis and suppress tumor proliferation either alone or in combination with chemotherapy across a variety of advanced solid malignancies [23–28]. What needs to be emphasized is that, the efficacy of apatinib is comparable to that of sorafenib or lenvatinib, but with more manageable safety profile and faster therapeutic response [26, 29–31].

Back to this case, the treatment of apatinib (orally 500 mg qd) [32] showed significant effect and least complications in a very short time. Just after treatment for 6 weeks and drug withdrawal for 10 days, a complete operation with total thyroidectomy, left central lymph node dissection and the muscular layer resection of the esophagus were performed. Tg detection and CT scan were applied to reassess the disease. Thankfully, there was no postoperative complication, such as wound dehiscence or fistula formation. At present, the role of TKIs is limited to those thyroid cancer cases that still progress after surgery, radioiodine or local ablation therapies. And there is no data to certify the use of antiangiogenic TKIs as neoadjuvant therapy in DTC. Thus, there are still many problems, including drug categories, dosage, time of adding medicine, withdrawal time before surgery and methods of disease reassessment, worthy to be further studied.

A recent article reported an initially unresectable, end-stage and BRAF-mutated ATC case, which responded well to combined medicine of dabrafenib, trametinib and pembrolizumab preoperatively, and then the tumor was completely resected [33]. Jennifer et al. illustrated that dabrafenib plus trametinib was feasible and effective as a neoadjuvant approach for locoregionally advanced BRAF^{V600E}-mutated ATC [19]. Furthermore, the therapy role is generally limited when a single chemotherapy is used in thyroid cancer. Hence, it is worth considering whether monotherapy or combination with conventional therapies are effective.

To our knowledge, this is the first report that VEGFR-2 TKI apatinib monotherapy was effective, safe and economical for unresectable locally advanced DTC preoperatively. The emergence of this neoadjuvant concept has changed the landscape of management to locally advanced TC. We believe that it's time to propose preoperative neoadjuvant targeted therapy for those inoperable DTCs to achieve extensive resection of extrathyroidal tissues and guarantee quality of life simultaneously. Yet, more cohort studies, randomized controlled trials and even related mechanism research are necessary.

**Abbreviations**

DTC: Differentiated thyroid cancer; PTC: Papillary thyroid cancer; TC: Thyroid cancer; FTC: Follicular thyroid cancer; HCTC: Hurthle cell thyroid cancer; RAI: Radioactive iodine; RLN: Recurrent laryngeal nerve; EBRT: External beam radiation therapy; ChT: Systemic chemotherapy; Tg: Thyroglobulin; CT: Computed tomography; MRI: Magnetic resonance imaging; gETE: Gross extrathyroidal extension; TKIs: Tyrosine
kinase inhibitors; MTC: Medullary thyroid cancer; ATC: anaplastic thyroid cancer; VEGF: Vascular endothelial growth factor

Declarations

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Authors’ contributions

YCZ and XZD contributed to the data collection and manuscript drafting. ZD was the major contributor of the design of the study. YQN, JZH, JK and BW were the patient’s surgeon and contributed to the data collection and analysis. ZLY, BMG, and YBF were substantially involved in data check and data analysis. All authors read and approved the revised manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Consent for publication

Informed written consent was obtained from the family of the patient for publication of this report and any accompanying images

Competing interests

The authors declare that they have no competing interests.

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**Figures**

Figure 1

H&E stain showed papillary growth pattern of the present PTC patient. a 200x, b 400x

Figure 2

Initial examinations revealed a huge left thyroid mass with esophageal stenosis and invasion (the red arrow indicates the esophagus while the blue arrow indicates the tumor). a CT scan, b MRI scan, c Esophagogastroduodenoscopy
Figure 3

CT imaging demonstrated improvement of esophageal compression and tumor reduction. a Scan after one month of apatinib, b Scan after 6 weeks of apatinib

Figure 4

Whole-body scan found no tumor bone metastasis after 6 months of operation.
Figure 5

Whole-body RAI scan revealed focal 131I uptake of the cervical thyroid bed.