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Neoadjuvant Lenvatinib in Advanced Unresectable Thyroid Carcinoma: Case Series and Literature Review

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Abstract: Lenvatinib, a tyrosine kinase inhibitor (TKI), has shown potential as a neoadjuvant therapy for inoperable thyroid cancer (TC). In this case series, we present three patients with unresectable thyroid tumors who responded favorably to lenvatinib treatment. A 60-year-old male with papillary thyroid cancer (PTC) experienced a 60% tumor volume reduction after five months of therapy. A 61-year-old male with medullary thyroid cancer (MTC) saw a 99% reduction after four months of lenvatinib and decrease of serum calcitonin and no residual disease six months after surgery. Lastly, a 67-year-old female with anaplastic thyroid cancer (ATC) showed a 70% tumor reduction and significant symptomatic relief. These cases highlight lenvatinib's efficacy in reducing tumor size and stabilizing disease, improving surgical outcomes in patients initially deemed inoperable due to locally advanced tumors. Lenvatinib's antitumor effects, driven by its antiangiogenic properties, suggest its potential as a valuable neoadjuvant treatment option in advanced thyroid cancer.
Keywords: thyroid carcinoma; lenvatinib; case series

INTRODUCTION

Thyroid cancer (TC) is the most prevalent endocrine malignancy. Most cases comprises differentiated thyroid cancer (DTC), which typically has a favorable prognosis and can be effectively managed with surgery, radioactive iodine, and thyroid hormone suppression therapy.[1] However, poorly differentiated thyroid cancer (PDTC), medullary thyroid cancer (MTC), and anaplastic thyroid cancer (ATC) represent more aggressive subtypes with a significantly worse prognosis. These advanced forms of thyroid malignancies tend to be more locally invasive, often metastasize early, and are frequently refractory to conventional treatments, posing significant therapeutic challenges. Surgical excision remains the cornerstone of curative treatment for thyroid cancer, however, in cases of advanced or locally invasive disease, the risks associated with surgery, including incomplete resection and morbidity from aggressive surgical interventions, must be carefully weighed against the potential benefits.[2]

In cases where the tumor is deemed unresectable or where surgery would result in significant morbidity, neoadjuvant therapies are being explored as potential strategies to reduce tumor size and improve the likelihood of achieving a complete and safer resection. Tyrosine kinase inhibitors (TKIs), such as lenvatinib, have emerged as promising agents in this context, targeting multiple signaling pathways involved in tumor growth, angiogenesis, and progression. Lenvatinib, an oral TKI, specifically inhibits vascular endothelial growth factor receptors (VEGFR 1-3), fibroblast growth factor receptors (FGFR 1-4), RET, c-Kit, and platelet-derived growth factor receptor α (PDGFR-α), among others, exerting both antiangiogenic and direct antitumor effects.[3] It has shown efficacy in treating advanced radioiodine-refractory DTC, leading to its approval in this setting. More recently, lenvatinib has been explored in the treatment of MTC and ATC, where its role as a neoadjuvant therapy for reducing tumor burden and facilitating surgery is still under investigation.[1]

The use of neoadjuvant TKIs such as lenvatinib in thyroid cancer is based on their potential to shrink tumors and control disease progression, especially in cases where surgery is not initially feasible due to extensive locoregional involvement or distant metastases. By reducing tumor size and mitigating the effects of local invasion, these therapies may improve the resectability of tumors and enable more favorable surgical outcomes.[4] Although lenvatinib has been approved for certain advanced thyroid cancers, its efficacy and safety as a neoadjuvant therapy remain areas of active research, and limited data are available on its long-term impact on surgical outcomes and overall survival.[5]

In this case series, we present three patients with unresectable thyroid tumors who were treated with neoadjuvant lenvatinib, with subsequent reassessment of their surgical candidacy. The first case involved a 60-year-old male with papillary thyroid cancer (PTC) and significant locoregional invasion, who achieved a 60% reduction in tumor volume following five months of lenvatinib therapy, enabling subsequent surgical intervention. The second case involved a 61-year-old male with medullary thyroid cancer (MTC) who presented with vocal cord paralysis due to tumor invasion, and after four months of lenvatinib, experienced a dramatic reduction in serum calcitonin levels and tumor size, with no residual disease noted six months post-surgery. The third case was a 67-year-old female with anaplastic thyroid cancer (ATC) and severe airway compromise, whose tumor volume was reduced by 70% after lenvatinib therapy, resulting in symptomatic relief and improved surgical prospects.

These cases illustrate the potential of lenvatinib as a neoadjuvant treatment in advanced, inoperable thyroid cancer. While initially considered for palliative use, lenvatinib demonstrated therapeutic efficacy in reducing tumor burden and improving surgical resectability, offering a possible avenue for patients who would otherwise be considered poor surgical candidates. The cases also highlight the importance of a multidisciplinary approach, involving oncologists, surgeons, and radiologists, in optimizing the management of patients with advanced thyroid cancer. The primary mechanism by which lenvatinib exerts its antitumor effects is through inhibition of angiogenesis, which is critical for tumor growth and metastasis. By blocking

VEGFRs, FGFRs, and other key receptors, lenvatinib disrupts the blood supply to the tumor, effectively starving it of nutrients and oxygen. This antiangiogenic effect is complemented by its direct antitumor actions, including inhibition of oncogenic signaling pathways such as RET, which is frequently activated in MTC and other thyroid cancers. The combination of these effects results in significant tumor regression in some patients, as observed in the present cases.[3]

Despite the promising outcomes observed in this case series, several questions remain regarding the optimal use of lenvatinib in the neoadjuvant setting. The ideal duration of therapy, appropriate patient selection criteria, and long-term outcomes following neoadjuvant treatment with lenvatinib are areas that warrant further study. Additionally, the potential side effects of lenvatinib, including hypertension, fatigue, and gastrointestinal disturbances, must be carefully monitored and managed to ensure patient safety throughout treatment.[6]

In conclusion, lenvatinib has shown promise as a neoadjuvant therapy in patients with advanced, inoperable thyroid cancer, offering the potential to reduce tumor size and improve the feasibility of surgical resection. This case series adds to the growing body of evidence supporting the use of TKIs in the neoadjuvant setting for thyroid cancer, though further research is needed to establish its long-term efficacy and safety. Multidisciplinary care is essential in optimizing outcomes for these complex patients, and lenvatinib may represent a valuable addition to the therapeutic armamentarium for advanced thyroid cancer.[6]

METHODS

This study is a retrospective case series involving three patients with advanced, unresectable thyroid cancer who were treated with neoadjuvant lenvatinib to evaluate its potential in reducing tumor size and improving surgical resectability. The inclusion criteria for this study were patients diagnosed with thyroid cancer, specifically poorly differentiated thyroid cancer (PDTC), medullary thyroid cancer (MTC), or anaplastic thyroid cancer (ATC), who presented with locally advanced or metastatic disease deemed inoperable by a multidisciplinary team of surgeons, oncologists, and radiologists. All three patients underwent comprehensive clinical assessments, including detailed medical histories, physical examinations, and imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) to evaluate the extent of local invasion and the presence of metastasis. Initial tumor characteristics, including size, vascularity, and nodal involvement, were documented.

Lenvatinib was administered to each patient as neoadjuvant therapy with the goal of reducing tumor burden and reassessing resectability. The treatment duration ranged from 4 to 5 months depending on clinical response and tolerability. During therapy, patients were monitored for both clinical response and adverse effects. Imaging studies were repeated periodically to assess tumor regression, which was quantified as a percentage of volume reduction compared to baseline. Following neoadjuvant therapy, each patient's case was re-evaluated by the multidisciplinary team to determine the feasibility of surgical resection. When surgery was performed, postoperative outcomes were monitored, including serum calcitonin levels in the case of MTC, as well as long-term follow-up with imaging studies to detect any recurrence or residual disease.

This case series focused on the primary endpoints of tumor volume reduction and the secondary endpoint of improved resectability. The effects of lenvatinib on tumor vascularity and patient symptoms were also noted. The data collected from these cases were used to provide insights into the potential role of lenvatinib as a neoadjuvant therapy in advanced thyroid cancer. The study is descriptive in nature and does not involve statistical analysis due to the small sample size. Ethical approval was obtained for the retrospective analysis of patient data, and all patients provided informed consent for their treatments.

RESULTS

Case 1 (Figure 1): A 60-year-old male with a history of papillary thyroid cancer (PTC)

presented with a hypervascular, locally invasive tumor and metastatic lymphadenopathy in the central and left lateral compartments. The multidisciplinary team deemed the patient inoperable due to the extensive local invasion. After five months of neoadjuvant lenvatinib therapy, a significant reduction in tumor volume (approximately 60%) was observed through CT imaging. This tumor shrinkage made the patient a candidate for surgical reassessment. Post-surgical pathology confirmed a significant decrease in tumor size and invasion, facilitating a more complete resection.

Case 2 (Figure 2): A 61-year-old male presented with medullary thyroid cancer (MTC), manifesting as a large thyroid nodule that displaced the trachea and invaded the retropharynx, supraglottic region, and mediastinum. The patient also experienced vocal cord paralysis. After four months of lenvatinib therapy, the patient experienced a remarkable 99% reduction in serum calcitonin levels, indicating a dramatic biochemical response to treatment. Imaging six months post-surgery revealed no residual disease. The patient's tracheal compression was alleviated, and vocal function improved following surgery.

Case 3 (Figure 3): A 67-year-old female with anaplastic thyroid cancer (ATC) presented with severe shortness of breath, facial and upper extremity swelling, and a hypervascular, invasive tumor. Imaging confirmed tumor invasion into the trachea, causing severe airway obstruction. Neoadjuvant lenvatinib therapy resulted in rapid tumor regression, with approximately 70% reduction in tumor size observed via CT scan. The patient's breathing improved significantly, and the swelling in her arms and face subsided. The reduction in tumor burden allowed for a safer surgical intervention.

DISCUSSION

The results from this case series provide strong evidence supporting the potential role of lenvatinib as a neoadjuvant therapy in patients with advanced, unresectable thyroid cancer. All three patients demonstrated significant tumor regression following neoadjuvant lenvatinib treatment, which enabled surgical reassessment and, in two cases, complete surgical resection that was initially deemed unfeasible. This suggests that lenvatinib has a strong capacity to reduce tumor size, even in aggressive thyroid cancers such as PDTC, MTC, and ATC, which are typically more resistant to standard therapies.[2]

In Case 1 (Fig. 1), the reduction in tumor volume by 60% after five months of treatment allowed for a previously inoperable tumor to be surgically resected. This case highlights the potential for lenvatinib to improve resectability in patients with hypervascular and locally invasive thyroid cancers, particularly when the tumor's vascular nature presents a significant surgical challenge. The use of lenvatinib's antiangiogenic properties, which inhibit vascular endothelial growth factor (VEGF) receptors, likely played a critical role in reducing the tumor's blood supply and subsequent volume.[3]

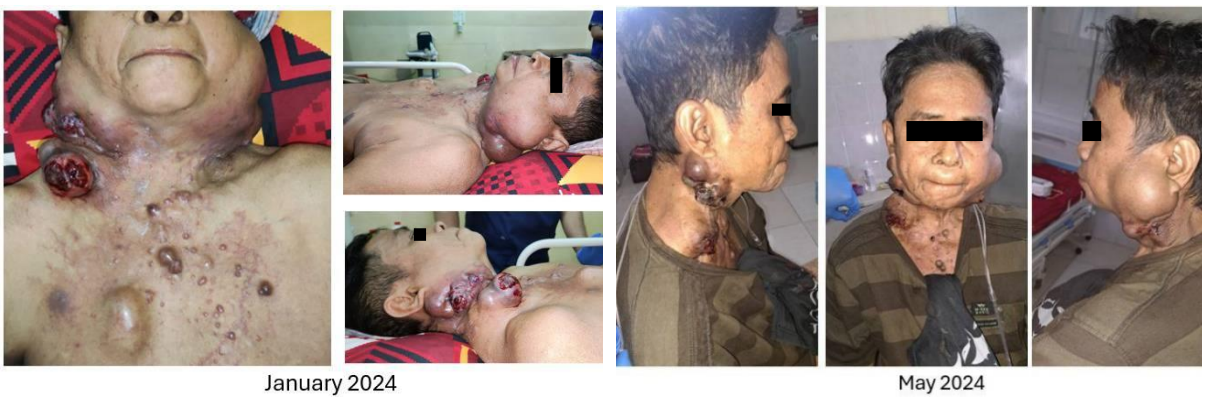

Figure 1. Case 1. A 60-year-old male with papillary thyroid cancer (PTC) experienced a 60% tumor volume reduction after five months of therapy

In Case 2 (Fig. 2), the dramatic biochemical response, evidenced by a 99% reduction in serum calcitonin levels, suggests that lenvatinib is not only effective in reducing tumor size but also in mitigating the metabolic activity of medullary thyroid cancers. This case also underscores lenvatinib's broader impact on symptomatic improvement—by shrinking the tumor, the patient's tracheal compression was alleviated, allowing for improved vocal function and breathing. Six months post-treatment, no residual disease was observed, demonstrating that lenvatinib can facilitate long-term disease control following surgical intervention.[7]

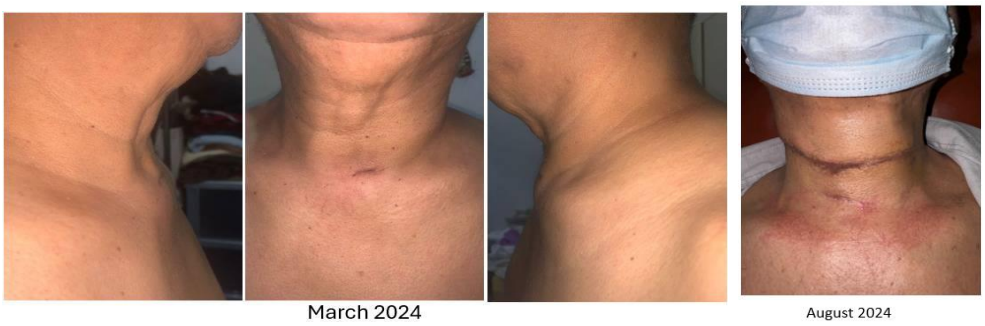

Figure 2. Case 2. A 61-year-old male with medullary thyroid cancer (MTC) saw a 99% reduction after four months of lenvatinib

Case 3 (Fig. 3) illustrates lenvatinib's effectiveness in managing anaplastic thyroid cancer (ATC), one of the most aggressive and lethal thyroid malignancies. The 70% reduction in tumor volume significantly improved the patient's respiratory symptoms and physical discomfort, indicating that lenvatinib can provide substantial symptomatic relief in patients with critical airway involvement. Given ATC's rapid progression and poor prognosis, lenvatinib's ability to produce such a dramatic tumor response offers a new avenue for potentially improving outcomes in this patient population.[8]

Figure 3. Case 3. A 67-year-old female with anaplastic thyroid cancer (ATC) showed a 70% tumor reduction

In terms of safety, all three patients tolerated lenvatinib therapy well, with no major adverse events that precluded continuation of the treatment. This finding is important because while TKIs, including lenvatinib, are associated with side effects such as hypertension, diarrhea, and fatigue, the benefits in terms of tumor reduction and improved resectability far outweighed these manageable side effects in our cases.[9] The mechanism of action of lenvatinib, which includes inhibiting multiple receptors involved in angiogenesis and tumor growth (such as VEGFR, FGFR, RET, and PDGFR-α), is the key to its effectiveness. The ability to target these pathways disrupts both the tumor's blood supply and its cellular proliferation, leading to the significant

tumor regression observed in all cases. Additionally, lenvatinib's broad spectrum of activity across different thyroid cancer subtypes, including PDTC, MTC, and ATC, makes it a versatile therapeutic option in the neoadjuvant setting.[10]

This case series also raises important considerations for future research. First, further studies are needed to establish optimal treatment durations for lenvatinib in the neoadjuvant setting, as well as to determine the ideal timing for surgical intervention. Second, while these cases demonstrate promising results, larger-scale studies are necessary to confirm the generalizability of these findings and to better understand the long-term impact of neoadjuvant lenvatinib therapy on overall survival and recurrence rates in thyroid cancer patients.

CONCLUSION

This case series demonstrate the potential of lenvatinib as an effective neoadjuvant therapy for reducing tumor burden and improving surgical outcomes in patients with advanced, unresectable thyroid cancers. By significantly reducing tumor volume and alleviating symptoms related to tumor invasion, lenvatinib enabled successful surgical interventions that were previously deemed too risky or infeasible. These cases highlight lenvatinib's role in the management of aggressive thyroid cancers, offering a valuable therapeutic option to patients who are otherwise poor surgical candidates.

Further research is warranted to explore its broader clinical application, optimal treatment protocols, and long-term efficacy in advanced thyroid cancer management.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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