CANCER DIAGNOSIS & PROGNOSIS
5: 127-131 (2025) doi: 10.21873/cdp.10421

Successful Salvage of Four Cases of Unresectable Papillary Thyroid Cancer Following Lenvatinib Administration

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Abstract. *Background/Aim: The role of lenvatinib as neoadjuvant chemotherapy for patients with advanced thyroid cancer has not been firmly established. In some cases, surgery may be considered when lenvatinib treatment becomes challenging to continue. Case Report: We present four cases of unresectable thyroid cancer diagnosed histologically as papillary carcinoma. The patients were a 61-year-old female (T4aN1bM0), a 75-year-old male (T4aN1bM0), a 61-year-old female (T3N1bM0), and a 64-year-old female (T4aN1bM0). Initial lenvatinib doses were 24, 10, 24, and 14 mg/day, respectively. The treatment administration periods were 8, 29, 3, and 6 months, with final doses of 4, 4, 10, and 14 mg/day, respectively. Tumors had primarily invaded the surrounding tissues, mainly the common carotid artery, and were considered unresectable. After lenvatinib administration, tumor shrinkage was observed. Despite complications from lenvatinib that resulted in difficulty in the administration of the drug, successful tumor resection was achieved, and local control was achieved in all patients. Conclusion: Preoperative lenvatinib treatment may offer a less invasive alternative for advanced thyroid cancer cases that would otherwise require invasive surgery.*

Differentiated thyroid cancer generally has a favorable prognosis when completely resected, making surgery the standard initial treatment (1, 2). In contrast, for advanced thyroid cancer, the extent of invasion into critical neck structure – including the trachea, esophagus and large vessels – plays a crucial role in determining treatment strategies (3). In some cases, surgery may be deemed inappropriate due to potential postoperative functional impairments (3).

Lenvatinib is a molecularly targeted antitumor agent that inhibits several receptor/tyrosine kinases, including the tyrosine kinase inhibitor of vascular endothelial growth factor receptor 1 (VEGFR1), VEGFR2, VEGFR3, fibroblast growth factor receptor 1 (FGFR1), FGFR2, FGFR3, FGFR4, platelet-derived growth factor a, RET proto-oncogene, and v-kit Hardy-Zuckerman 4 feline sarcoma virus oncogene homolog (4-6). Since its introduction in 2015, lenvatinib has demonstrated effectiveness in treating unresectable differentiated thyroid cancer (7, 8). Although lenvatinib is associated with high response rates and improved overall and progression-free survival, complete cures with lenvatinib alone are uncommon (7, 8). Furthermore, side-effects of using lenvatinib, such as hypertension, can substantially affect the quality of life (QOL) of patients. Despite various measures, such as dose adjustments or scheduled drug holidays, prolonged lenvatinib therapy may be challenging (9). However, in some cases, thyroid cancer previously deemed unresectable may become resectable due to tumor shrinkage induced by lenvatinib treatment. For example, Iwasaki et al. reported that lenvatinib can be used as neoadjuvant chemotherapy (NAC), with a high response rate and rapid therapeutic effect (10). Although the use of lenvatinib as NAC is not yet well-established, surgery may be considered in situations where it is difficult to continue lenvatinib treatment. Here, we report four cases of initially unresectable thyroid cancer that were successfully resected following lenvatinib treatment.

Case Report

This retrospective review of patient medical records was conducted in accordance with the ethical guidelines set forth by the responsible committee on human experimentation (both institutional and national) and adhered to the principles outlined in the Declaration of Helsinki (1975, revised 2008) (11). This study was approved by our Institutional Review

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Key Words: Papillary carcinoma, thyroid cancer, advanced stage, unresectable, lenvatinib, salvage surgery.

Table I. *Characteristics of patients who underwent salvage surgery after lenvatinib administration.*

	Case			
Factor	1	2	3	4
Sex	Female	Male	Female	Female
Age, years	61	75	61	64
TNM	T4aN1bM0	T4aN1bM0	T3N1bM0	T4aN1bM0
Pathology	Papillary carcinoma			
Infiltrating organ	CCA, trachea	CCA, larynx, esophagus	CCA, pleura	CCA
Initial lenvatinib dose, mg	24	10	24	14
Duration of lenvatinib administration, months	8	29	3	6
Side-effects	Hypertension, proteinuria	Diarrhea, proteinuria	Hypertension, proteinuria	-
Final lenvatinib dose, mg	4	4	10	14
Preoperative lenvatinib withdrawal, day	7	10	20	13
Postoperative lenvatinib dose, mg	-	4	-	-
Pre-treatment Tg, ng/ml	727	1,120	TgAb (+)	1,440
Post-treatment Tg, ng/ml	23.6	2.8		26.9

CCA: Common carotid artery; Tg: thyroglobulin.

Board (MH2020-209). Written informed consent was obtained from all the patients.

Lenvatinib treatment was initiated at our Department in 2016. Although lenvatinib was primarily used for patients with metastatic lesions, including those in the lungs and bone, it was also employed in patients who were unable to undergo total thyroidectomy.

Preoperative diagnostic procedures included histopathological evaluation and diagnostic imaging studies. Fine-needle aspiration cytology with/without open biopsy under local anesthesia were performed to obtain tissue samples from thyroid tumors. Histopathological diagnosis was considered for most tumors before initiating therapy. Computed tomography (CT) was performed to assess the thyroid tumors and neck region. For patients with suspected or confirmed malignant tumors, 18F-fluorodeoxy glucose positron-emission tomography was employed to detect distant metastases such as bone metastases.

Criteria for determining the infeasibility of radical resection included tumor invasion into the carotid artery, larynx, esophagus, or pleura. Following the initiation of lenvatinib treatment, tumors were monitored monthly using ultrasound or CT. Surgery was performed when it was difficult to continue lenvatinib administration, and resection was deemed feasible based on imaging results, primarily CT.

The starting dosage of lenvatinib was 24 mg/day. However, due to hypertension, two patients received lenvatinib at an initial dose of 24 mg/day, while the other two patients were started on 14 and 10 mg/day, respectively.

Case presentation. The characteristic features of the patients are summarized in Table I.

Case 1: A 61-year-old woman with no significant medical history was diagnosed with papillary thyroid carcinoma based on an open biopsy of the tumor. The tumor had invaded the trachea and surrounding major blood vessels [Figure 1 A(i)], making radical resection challenging. Lenvatinib was administered at a dose of 24 mg/day. Despite tumor shrinkage, the lenvatinib dosage was gradually reduced due to hypertension and other side-effects from 24 to 4 mg/day in 8 months. Because the side-effects were difficult to manage, lenvatinib treatment was discontinued. Based on the CT images obtained at that time [Figure 1 A(ii)], we determined that the tumor was resectable, and total thyroidectomy was performed 7 days after discontinuation of lenvatinib. The patient underwent radioactive iodine (RAI) treatment post-surgery, and no disease progression has been observed to date, 7 years and 7 months after surgery.

Case 2: A 75-year-old man with a history of hypertension and Fisher syndrome was diagnosed with papillary thyroid carcinoma based on cytological findings. CT imaging revealed that the tumor and metastatic lymph nodes completely surrounded the right common carotid artery [Figure 1B(i)]. Radical resection was impossible due to tumor invasion into the larynx and esophagus. Lenvatinib was administered at a dose of 10 mg/day, with dosage adjustments for side-effects and therapeutic response. However, management of side-effects proved difficult, leading to discontinuation of lenvatinib 29 months after its initiation. CT images obtained at that time [Figure 1B(ii)] indicated that the tumor had become resectable, and total thyroidectomy was performed 10 days after the cessation of lenvatinib. Postoperative RAI treatment was followed by the emergence of multiple lymph node recurrences in the neck 6 months later. Despite possible lenvatinib resistance, the lymph nodes shrank after restarting lenvatinib at 4 mg/day.

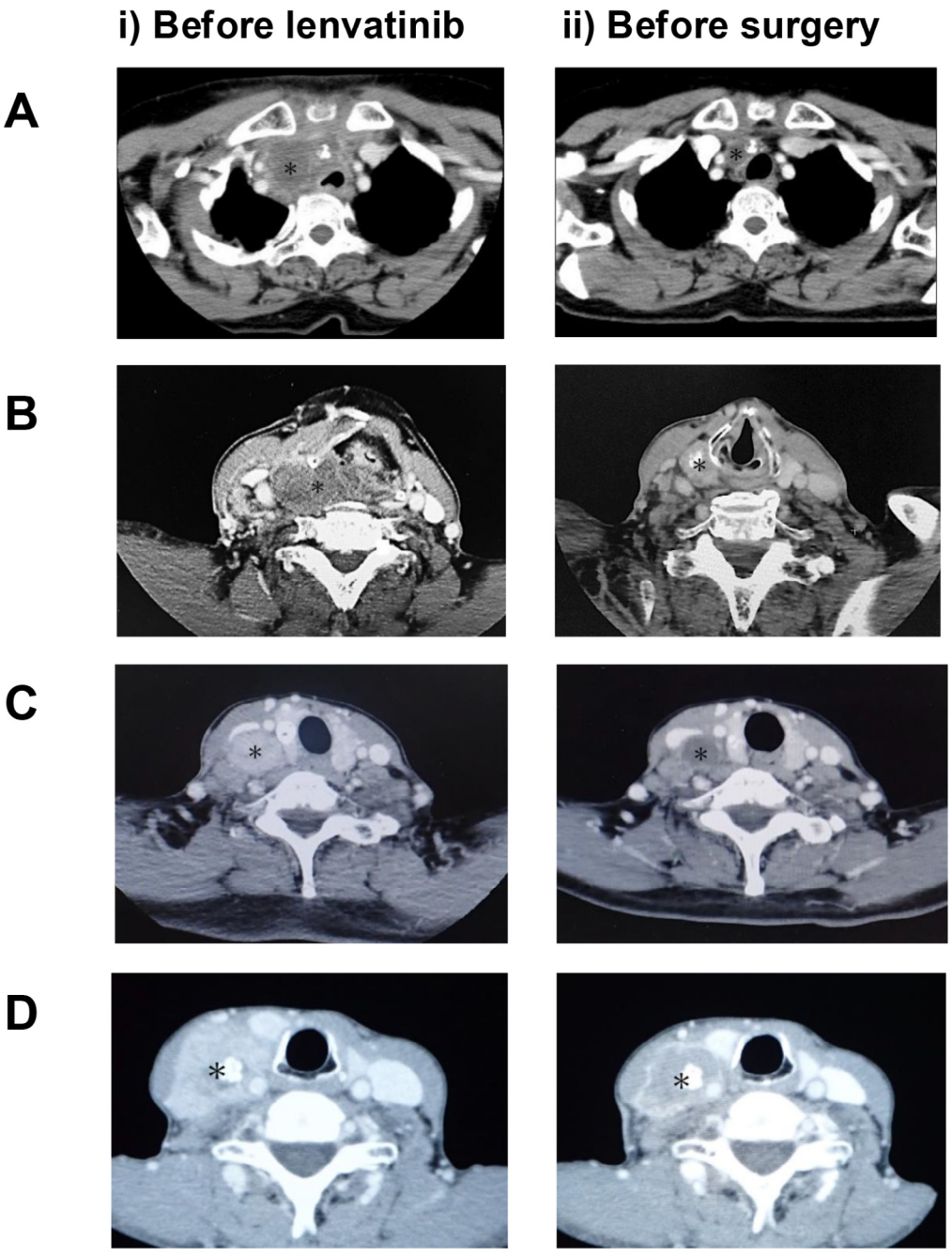

Figure 1. *Computed tomography images before lenvatinib treatment (left) and (right) before surgery (left) for cases 1 to 4 (A-D), respectively. The asterisks indicate the target lesions. In each case, lenvatinib treatment was effective, resulting in tumor shrinkage or cystic degeneration.*

To date, no significant side-effects or further recurrences have been reported, 31 months after surgery.

Case 3: A 61-year-old woman with no significant medical history was diagnosed with papillary thyroid carcinoma based on an open biopsy of the right cervical lymph node. The tumor appeared to invade major blood vessels and the pleura [Figure 1C(i)], making radical resection difficult. Lenvatinib was administered at a dose of 24 mg/day. Although the tumor was reduced, the lenvatinib dosage had to be gradually lowered due to side-effects. Because it was difficult to control the side-effects, lenvatinib was discontinued 3 months after its initiation. Based on CT images obtained at that time [Figure 1C(ii)], we

determined that the tumor was resectable, and total thyroidectomy was performed 20 days after the cessation of lenvatinib. The patient underwent RAI treatment post-surgery, and no disease progression has been observed to date, 31 months after surgery.

Case 4: A 64-year-old woman with no significant medical history had a core-needle biopsy which confirmed papillary thyroid cancer. Physical findings and CT images indicated that radical resection was difficult [Figure 1D(i)], and lenvatinib was initiated at 14 mg/day. Few side-effects were observed and lenvatinib led to tumor shrinkage. Based on CT images [Figure 1D(ii)], the tumor was determined to be resectable 6 months after the initiation of lenvatinib administration; total thyroidectomy was performed 13 days after the cessation of lenvatinib. Due to a shortage of iodine preparations, postoperative RAI treatment was not possible; instead, external radiotherapy was administered to the neck. To date, no recurrence has been reported, 22 months after surgery.

In our series of patients, the mean starting dose of lenvatinib was 15.5 mg/day (range=10-24 mg/day). Considering the tumor progression and individual medical history, not all patients were able to start treatment at the maximum dosage of 24 mg lenvatinib. The duration of lenvatinib administration before surgery varied, with an average of 11.5 months. The mean preoperative lenvatinib dose was 8 mg/day, and the mean preoperative lenvatinib withdrawal period before surgery was 12.5 days. Tumor regrowth was noted in one patient during this period. There were no severe postoperative complications such as bleeding or poor wound healing. Lenvatinib was resumed postoperatively in one patient (case 2).

Discussion

Lenvatinib is typically used to treat unresectable thyroid cancer that is resistant to RAI therapy after total thyroidectomy (9). According to the lenvatinib package insert, its efficacy and safety have not been established in patients who have not received RAI treatment or those who have not undergone total thyroidectomy. However, in clinical practice, lenvatinib may be necessary in cases where radical resection is difficult. Even in the absence of tumor-related symptoms, considering factors, such as patient age and sites of metastases, early introduction of lenvatinib may improve patient prognosis (12). Therefore, some reports suggest that physicians should not hesitate to use lenvatinib in patients without a history of RAI treatment [reviewed in (13)]. However, side-effects associated with the use of lenvatinib, which affects the QOL of patients, make long-term administration challenging. In such situations, initially unresectable thyroid tumor may become resectable as the tumor shrinks following lenvatinib treatment. Recently, there has been a gradual increase in reports of surgery following lenvatinib administration (10, 14-17). The literature indicates that the average starting dose of lenvatinib is 17.8 mg, which is higher than that in our patients. Our patients underwent surgery when it became difficult to continue lenvatinib; however, in several reports, most patients underwent surgery when tumor shrinkage was insufficient (10, 14-17). The average duration of lenvatinib use before surgery was reported as 5.5 months, which was shorter than that in our cases. The average dose immediately before surgery was 12.7 mg (10, 14-17), higher than that in our patients. This difference may be due to the fact that the patients in those reports underwent surgery when the tumor had stopped shrinking, while lenvatinib was continued until it became difficult to use. The preoperative lenvatinib withdrawal period has been reported to be 11.1 days (10, 14-17), which was consistent with our cases. During the drug withdrawal period, bilateral recurrent laryngeal nerve paralysis occurred in one patient who required emergency surgery (10). No postoperative complications were observed in the reported cases, and lenvatinib was discontinued in all cases (10, 14-17).

In summary, after starting lenvatinib treatment for unresectable thyroid cancer, surgery was considered to be appropriate when the tumor had stopped shrinking or when it became difficult to continue lenvatinib treatment. It appears that no issues arise if the preoperative drug withdrawal period exceeds 2 weeks. However, due to concerns about complications during lenvatinib withdrawal, a 1-week withdrawal period may be preferrable. No postoperative complications have been reported, suggesting that surgery can be performed relatively safely in such cases. However, even though the tumor may shrink, surgery remains difficult in these cases. Given the high-risk of postoperative functional impairment and complications, careful consideration is needed to determine the appropriateness of surgery. Therapy with lenvatinib plays a major role in avoiding the significant functional impairments associated with surgery for locally advanced thyroid cancer, such as laryngectomy, tracheostomy, and esophageal reconstruction. Furthermore, when considering the QOL of the patient, cessation of lenvatinib after surgery is beneficial for eliminating its side-effects. Our study also demonstrated the possibility of restarting and continuing low-dose lenvatinib post-surgery, even when preoperative administration was difficult. Future studies should focus on management methods by analyzing more patients to minimize the incidence of lenvatinib side-effects and determine the optimal preoperative dosage, duration of use, withdrawal period, and timing of surgery.

Conclusion

Along with a literature review, we reported four cases of papillary thyroid cancer initially deemed unresectable which were subsequently managed with surgery after lenvatinib treatment. Although lenvatinib has high clinical efficacy, complete cure with this drug alone is difficult. A combination of lenvatinib and surgery, following thorough patient counseling

and careful pre- and postoperative management, may offer the potential for complete cure. Given the frequent need to reduce lenvatinib dosage or discontinue the drug owing to side-effects, timely surgery may be effective. The use of lenvatinib as NAC has not been established, necessitating careful case selection. Further prospective studies are needed to clarify the efficacy of preoperative lenvatinib treatment for advanced thyroid cancer requiring invasive surgery.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization: KS; methodology: KS and KT; investigation: KT; resources: KT, KS, KK, DS, SO, AI, JM and TK; writing – original draft preparation: KT and KS; funding acquisition: KS, KK and DS. All Authors have read and agreed to the published version of the article.

Acknowledgements

The Authors would like to thank Editage (www.editage.com) for the English language editing.

Funding

This study was supported in part by JSPS KAKENHI, Grant Number 26462619.

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Received October 13, 2024
Revised November 8, 2024
Accepted November 11, 2024