Prognostic significance of lung metastasis-related finding in lenvatinib treatment for differentiated thyroid cancer

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Abstract
Purpose This study aimed to analyze the clinical course of patients with differentiated thyroid cancer (DTC) who were treated by lenvatinib and investigate the specific criteria for the initiation of lenvatinib in lung metastasis.

Methods A total of 111 patients with DTC treated by lenvatinib were included in the study. Patients were divided into two groups based on the target lesion for the initiation of lenvatinib: lung metastasis group and other metastases group.

Results In the univariate analysis, the tumor size for the lung metastasis (p = 0.002) and the factor of lung metastasis group (p < 0.001) were significantly associated with overall survival (OS). Multivariate analysis revealed that the factor of lung metastasis group [hazard ratio, 0.408; 95% confidence interval (CI), 0.206–0.810; p = 0.010] was the only independent prognostic factor of OS. Of the 53 patients in the lung metastasis group, 12 (23%) had lung metastasis-related finding such as pleural effusion (n = 12), hemoptysis (n = 2), and dyspnea (n = 1) at the initiation of lenvatinib treatment. The median OS in patients with or without lung metastasis-related findings were 41.0 [95% CI, 10.4–not available (NA)] months and 62.9 (95% CI, 53.0–NA) months, respectively (p = 0.022).

Conclusion Patients with lung metastasis-related finding at the initiation of lenvatinib treatment had a poorer prognosis among the lung metastasis group. It is important to consider not only the tumor size but also the presence of lung metastasis-related findings when initiating lenvatinib treatment for DTC patients with lung metastasis.

Keywords Differentiated thyroid cancer • Distant metastasis • Lenvatinib • Prognosis

Introduction
Thyroid cancer is the most common type of endocrine-related malignancy [1]. Papillary thyroid cancer and follicular thyroid cancer are types of differentiated thyroid cancer (DTC), and they account for >90% of all thyroid cancers [2]. DTC has a good prognosis, with a diseasespecific survival rate >90% [2]. However, some patients with DTC experience recurrence or persistent disease, and the prognosis of patients with unresectable and advanced DTC remains poor [3].

In American Thyroid Association guidelines, kinase inhibitor therapy such as lenvatinib should be considered in patients with radioactive iodine (RAI)-refractory DTC complicated with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease [4]. Lenvatinib causes inhibition of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, and platelet-derived growth factor receptor α, and RET and KIT signaling networks. The global Phase 3 Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) reported a significant antitumor effect of lenvatinib [5]. Previous studies have revealed that lenvatinib treatment has some prognostic factors, such as tumor volume, performance status (PS), and neutrophil-to-lymphocyte ratio [6–8]. Although lenvatinib has significant efficacy for thyroid cancer treatment, the incidence of adverse events (AEs) is very high, especially in the Japanese population [9].
Some patients with DTC with smaller lung metastasis probably have better prognosis even though they do not undergo lenvatinib treatment [10]. Therefore, the harm of AE may be greater than the benefit of lenvatinib treatment when the initiation of lenvatinib is determined simply by the progressive tumor size. Thus, this study aimed to analyze the clinical course of patients with DTC who were treated by lenvatinib and investigate the specific criteria for the initiation of lenvatinib treatment in lung metastasis.

Materials and methods

Study participants

The protocol of this retrospective study was approved by the Institutional Review Board of Kanagawa Cancer Center (IRB approval no. 2022-4). We retrospectively identified 111 patients with DTC treated by lenvatinib at Kanagawa Cancer Center from May 2015 to March 2022. Written informed consent was obtained from all patients before inclusion in the study. The inclusion criteria were DTC confirmed by histology, previous total thyroidectomy, age ≥18 years, and use of RAI before lenvatinib treatment. The exclusion criteria were medullary thyroid cancer, anaplastic thyroid cancer, and other recurrent or concurrent malignancies. The following demographic and clinicopathological data were collected for analysis: age, sex, PS, histological type of thyroid cancer, initial lenvatinib dose, clinical response to lenvatinib, overall survival (OS) duration, and AEs. The initial lenvatinib dose was 24 mg/day, and it was adjusted according to the occurrence of AEs. However, some patients started the initial low dose of lenvatinib because of older age or comorbidities [11]. Among 111 patients, 95 were treated by lenvatinib as first line treatment. The remaining 16 patients were treated by lenvatinib as second line treatment and their first line treatment were sorafenib. Patients were divided into two groups based on the site of metastases that led to the initiation of lenvatinib: lung metastasis group and other metastases group. Patients with lung metastasis group started lenvatinib for the progression of lung metastasis. Patients with other metastases group started lenvatinib for the progression other than lung metastasis such as bone, lymph node, or local recurrence.

Definitions

The efficacy evaluation of lenvatinib was conducted according to the RECIST1.1 criteria, including complete response, partial response (PR), stable disease, and progressive disease [12]. The objective response rate was defined as the proportion of patients with complete or PR. The diameter of all target lesions was 10 mm or more. OS was calculated as the time from the start of lenvatinib treatment to the date of death from any cause. AEs were evaluated using the Common Terminology Criteria for Adverse Events, version 5.0.

Statistical analysis

All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Specifically, EZR is a modified version of R commander designed to add statistical functions used frequently in biostatistics [13]. Categorical variables were compared using Fisher’s exact test, and continuous variables were compared using the Mann–Whitney U test. OS curves were constructed using the Kaplan–Meier method. The Cox proportional hazards model was used to determine OS-associated factors. All p values <0.05 were considered significant. Survival analysis was determined using the final examination date confirmed using the medical records of the study participants.

Results

Baseline characteristics

Table 1 shows baseline characteristics. The study included 44 male and 67 female patients, with a median age of 72 (range, 35–91) years and median tumor size for target lesion of 25 (range, 10–99) mm. The lung metastasis group had 53 patients and other metastases group had 58 patients, respectively. Among 111 DTC patients treated by lenvatinib, 56 (50%), 17 (15%), 21 (19%), 12 (11%), 4 (4%), and one (1%) started lenvatinib with a dose of 24, 20, 14, 10, 8, and 4 mg, respectively. A significant difference in the tumor size for the target lesion was found between the lung metastasis group and other metastases group (p <0.001). On the contrary, other factors including sex, age, histology, PS, initial lenvatinib dose, thyroglobulin concentration, and positive rate of anti-thyroglobulin antibody were not significantly different between the two groups.

Efficacy and AEs

Table 2 shows treatment outcomes. The response rates in the lung metastasis and other metastases groups were 68% and 45%, respectively (p = 0.021). No significant differences were noted in the incidences of hypertension, proteinuria, fatigue, anorexia, diarrhea, palmar–plantar erythrodysesthesia syndrome, liver dysfunction, and oral mucositis, which are common AEs of lenvatinib, between the two groups (Table 3).
Analysis of OS

The median OS for all 111 patients was 34.9 [95% confidence interval (CI), 22.3–53.5] months. Table 4 exhibits the results of the univariate and multivariate analyses of OS-associated factors. In the univariate analysis, the tumor size for the target lesion \( p = 0.002 \) and the factor of lung metastasis group \( p < 0.001 \) (Fig. 1) were significantly associated with OS. These factors were further analyzed using multivariate analysis, which revealed that the factor of lung metastasis group (hazard ratio, 0.408; 95% CI, 0.206–0.810; \( p = 0.010 \)) was the only independent prognostic factor of OS (Table 4).

Clinical course and outcome in the lung metastasis group

Since the factor of lung metastasis group was the only independent prognostic factor on lenvatinib treatment, the clinical course and outcome were examined in the lung metastasis group. Table 5 and Fig. 2 show the detailed clinical data in the lung metastasis group. Of the 53 patients...
in the lung metastasis group, 20 (38%) had lung metastasis upon the diagnosis of thyroid cancer. The tumor size for lung metastasis upon diagnosis was <10 mm in 32 (67%) patients. The median duration between the diagnosis of lung metastasis and the initiation of lenvatinib treatment was 57.1 (1.0–148.9) months (Fig. 2). Furthermore, 12 (23%) had lung metastasis-related findings such as pleural effusion (n = 12), hemoptysis (n = 2), and dyspnea (n = 1) at the initiation of lenvatinib treatment. The median duration between the diagnosis of lung metastasis and the initiation of lenvatinib treatment was 57.1 (1.0–148.9) months (Fig. 2). Therefore, lung metastasis-related finding was a negative prognostic factor in the lung metastasis group. Of the 32 patients with tumor size <10 mm upon the diagnosis of distant metastasis, the median duration between the diagnosis of lung metastasis (<10 mm) and the tumor size became ≥10 mm was 35.8 (4.0–137.3) months. Additionally, the median duration between the tumor size became ≥10 mm and the initiation of lenvatinib treatment was 22.1 (0–70.6) months in these 32 patients. Although these 32 patients started lenvatinib at a median tumor size of 17 mm, the median OS in lenvatinib treatment was good at 53.8 [95% CI, 26.0–not available (NA)] months (Table 5).

### Discussion

This study examined the clinical course of patients with DTC who received lenvatinib treatment and investigated the specific criteria for the introduction of lenvatinib treatment in lung metastasis. The study showed that patients with lung metastasis group had significantly better prognosis regardless of other parameters. Furthermore, the median OS was good at 62.9 months in the lung metastasis group even though the median tumor size of lung metastasis at the time of lenvatinib treatment initiation was 17 mm. However, patients with lung metastasis-related findings at lenvatinib treatment initiation had a poorer prognosis compared with patients without lung metastasis-related findings in lung metastasis group. Therefore, lung metastasis-related finding was considered to be a negative prognostic factor in the lung metastasis group.

The first result of SELECT by Schlumberger et al. showed that a median progression free survival (PFS) duration following lenvatinib treatment was 18.3 months [5]. Additionally, Gianoukakis et al. revealed prolonged PFS (33.1 months) in lenvatinib responders [14]. Therefore, it is important to identify responders for predicting prognosis. Previous studies have reported that some parameters including patients’ age were associated with OS following lenvatinib treatment [6–8, 15]. However, in this study, no correlation was found between such patient’s baseline characteristics and OS. Furthermore, the factor whether lenvatinib was initiated for lung metastasis or other metastases was the only independent prognostic factor. Since patients with thyroid cancer complicated with lung metastasis had generally better prognosis than patients with other metastases such as bone [16], liver [17], and brain [18], it

| Efficacy Evaluation            | Lung metastasis group (n = 53) | Other metastases group (n = 58) | p value |
|-------------------------------|--------------------------------|--------------------------------|---------|
| Efficacy evaluation           |                                |                                |         |
| Complete response             | 0                              | 1 (2%)                         |         |
| Partial response              | 36 (68%)                       | 25 (43%)                       |         |
| Stable disease                | 13 (24%)                       | 26 (45%)                       |         |
| Progressive disease           | 1 (2%)                         | 5 (8%)                         |         |
| Not evaluable                 | 3 (6%)                         | 1 (2%)                         |         |
| Objective response rate       | 36 (68%)                       | 26 (45%)                       | 0.021   |

| Adverse events                | Lung metastasis group (n = 53) | Other metastases group (n = 58) | p value |
|-------------------------------|--------------------------------|--------------------------------|---------|
| Hypertension                  | 48 (90%)                       | 51 (88%)                       | 0.764   |
| Proteinuria                   | 34 (64%)                       | 35 (60%)                       | 0.7     |
| Fatigue                       | 19 (36%)                       | 22 (38%)                       | 0.846   |
| Anorexia                      | 21 (40%)                       | 29 (50%)                       | 0.34    |
| Diarrhea                      | 8 (15%)                        | 11 (19%)                       | 0.623   |
| Palmar-plantar erythrodysesthesia syndrome | 29 (55%) | 23 (40%) | 0.13    |
| Liver dysfunction             | 9 (17%)                        | 8 (14%)                        | 0.793   |
| Oral mucositis                | 6 (11%)                        | 5 (9%)                         | 0.755   |
Table 4  Analysis of factors associated with overall survival

| Variables                        | n = 111 | Univariate analysis p value | HR (95% CI) | Multivariate analysis p value (months) |
|----------------------------------|---------|-----------------------------|-------------|---------------------------------------|
| Sex                              |         |                            |             |                                       |
| Male                             | 44 (40%)| 0.547                       |             |                                       |
| Female                           | 67 (60%)|                            |             |                                       |
| Age (years)                      |         |                            |             |                                       |
| ≤65                              | 33 (30%)| 0.679                       |             |                                       |
| >65                              | 78 (70%)|                            |             |                                       |
| Histology                        |         |                            |             |                                       |
| PTC                              | 87 (78%)| 0.862                       |             |                                       |
| FTC or PDTC                      | 24 (22%)|                            |             |                                       |
| Performance status               |         |                            |             |                                       |
| 0                                | 83 (75%)| 0.255                       |             |                                       |
| ≥1                               | 28 (25%)|                            |             |                                       |
| Initial lenvatinib dose (mg)     |         |                            |             |                                       |
| 24                               | 56 (50%)| 0.42                        |             |                                       |
| <24                              | 55 (50%)|                            |             |                                       |
| Tumor size for target lesion (mm) |        | 0.002                       | 1.576 (0.834–2.978) | 0.161 | 0.001 |
| ≤25                              | 64 (58%)|                            |             |                                       |
| >25                              | 47 (42%)|                            |             |                                       |
| Target lesion group              |         | <0.001                      | 0.408 (0.206–0.810) | 0.010 | 0.010 |
| Lung metastasis group            | 53 (48%)|                            |             | 62.9 (95% CI, 41.0–not available)    |
| Other metastases group           | 58 (52%)|                            |             | 23.6 (95% CI, 17.0–34.1)             |

CI confidence interval, FTC follicular thyroid cancer, HR hazard ratio, OS overall survival, PDTC poorly differentiated thyroid cancer

*Median tumor size was 25 mm in all 111 patients

Fig. 1 Overall survival in patients with lung metastasis group and other metastases group. The median overall survival in patients with lung metastasis group and other metastases group were 62.9 [95% confidence interval (CI), 41.0–not available] months and 23.6 (95% CI, 17.0–34.1) months, respectively (p < 0.001)
might be reasonable that the criteria of lenvatinib initiation are determined by each target organ.

A previous study reported that patients with a pleural effusion survived a duration of 0.1–82.8 months and pleural effusion was the prognostic factor among patients with metastatic thyroid cancer [19]. Furthermore, the events of pleural effusion may predict bad prognosis during lenvatinib treatment [20]. Our study showed that patients with lung metastasis-related finding at lenvatinib treatment initiation had a poorer prognosis than those who did not. Sugino et al. also reported that the presence of a symptom was the only factor significantly related to poorer PFS and OS following lenvatinib treatment [21]. Therefore, it is important to start lenvatinib treatment before the occurrence of lung metastasis-related findings.

The initial lenvatinib dose of 24 mg/day in patients with thyroid cancer was determined by a phase II study [22]. However, higher toxicity was observed in the SELECT, especially in the Japanese population [5, 9]. We previously investigated a small population in a preliminary study that assessed the initial low dose of lenvatinib. The study indicated that the initial low dose of lenvatinib may be allowed for patients with older age or comorbidities [11]. On the contrary, a randomized study of lenvatinib 18 mg/day vs. 24 mg/day in patients with DTC revealed that a starting lenvatinib dose of 18 mg/day did not demonstrate non-inferiority compared to a starting dose of 24 mg/day. Therefore, the study concluded that the appropriate initial dose of lenvatinib was 24 mg/day [23]. In this study, no significant difference was found in the OS by the initial dose of lenvatinib. One reason is that racial difference may affect the efficacy and metabolism of lenvatinib [24–26]. The blood plasma concentration of lenvatinib and patient characteristics may need to be considered to determine the appropriate dose [27, 28]. The previous reports indicated that the incidence of AEs did not decrease when patients treated with initial low dose of lenvatinib compared with full dose, and the incidence of AEs was also high in this study even though the half of patients started initial low dose of lenvatinib [11, 23].

In the subgroup analysis of SELECT, the median OS in patients with baseline lung metastasis of ≥10, 15, and 20 mm were 44.7, 44.1, and 34.7 months, respectively [6]. The study concluded that the early initiation of lenvatinib treatment may improve outcomes in patients with radioiodine-refractory DTC and lung metastasis of ≥10 mm [6]. On the contrary, the result of our study showed that the median OS of the lung metastasis group was good at 62.9 months even though the median tumor size for the target lesion was 17 mm, which was larger than the size of 10 mm. Furthermore, the median duration from when the lung metastasis became 10 mm to the start of lenvatinib treatment was 22.1 (95% CI, 0–70.6) months in patients with DTC whose lung metastasis diameter at the time of diagnosis of distant metastasis was <10 mm. Since the incidence of AE of lenvatinib was very high, especially in the Japanese population [5, 9], very early administration of lenvatinib is likely to be harmful. The difference in the results between our study and those of a previous subgroup analysis might have been due to the difference in the study population. Our study analyzed patients who received lenvatinib for the target lesion of lung metastasis. On the contrary, a previous study analyzed patients with DTC with any lung metastasis regardless of target or nontarget lesions [6]. In DTC patients with lung metastasis, it is important not only to determine lenvatinib treatment initiation simply based on the tumor size but also to consider the previous clinical course, life prognosis, and wishes of the patient.

Taylor et al. revealed that lower PS provide prognostic value for improved efficacy in patients with RAI-refractory DTC [8]. However, patients with PS ≥1 had better OS

Table 5 Clinical data in lung metastasis group

| All patients in lung metastasis group | n = 53 |
|--------------------------------------|-------|
| Lung metastasis upon the diagnosis of thyroid cancer |       |
| Yes | 20 (38%) |
| No  | 33 (62%) |
| Tumor size for lung metastasis upon the diagnosis (mm), median (range)c | 7 (3–27) |
| <10 | 32 (67%) |
| ≥10 | 16 (33%) |
| Lung metastasis-related finding |       |
| Pleural effusion | 12 (23%) |
| Dyspnea     | 1 (2%)  |
| Duration between the diagnosis of lung metastasis and initiation of lenvatinib (months), median (range) | 57.1 (1.0–148.9) |
| Patients with tumor size of <10 mm upon the diagnosis of lung metastasis in lung metastasis group | n = 32 |
| Tumor size for lung metastasis at the initiation of lenvatinib (mm), median (range)f | 17 (10–35) |
| Duration between the diagnosis of lung metastasis (<10 mm) and tumor size became ≥10 mm (months), median (range) | 35.8 (4.0–137.3) |
| Duration between tumor size became ≥10 mm and the initiation of lenvatinib (months), median (range) | 22.1 (0–70.6) |
| Overall survival in lenvatinib treatment (months), median (range) | 53.8 (26.0–NA) |

NA not available

aData were unknown in five patients

bData were unknown in one patient
compared with patients with \( PS = 0 \) in this study even though there was not statistically different. The median follow-up time was 15 months in patients with \( PS = 0 \) and 47 months in patients with \( PS \geq 1 \). We think that the short observation period interfered in measuring the true OS time of patients with \( PS = 0 \).

This study has some limitations. First, this was a single-center, nonrandomized, retrospective study that included a small number of patients. Second, some data such as thyroglobulin concentration in one patient, tumor size for lung metastasis upon the diagnosis in five patients, and duration between the diagnosis of lung metastasis and initiation of lenvatinib in one patient were unknown because those patients were initially treated in other institutions. Finally, the biomarker analysis was not performed in our study. The lung metastasis group may have better histological nature than the other metastases group [29, 30]. Despite these limitations, we believe that the results of our study contribute to the understanding of the clinical course and outcome in patients with DTC treated with lenvatinib. Our results may also contribute the information to determine the timing of lenvatinib initiation by the clinicians and for the patients who have concerns about starting tyrosine kinase inhibitor.

In conclusion, target lesion was the only independent prognostic factor of OS following lenvatinib treatment. Therefore, compared with the other metastases group, the lung metastasis group had a better prognosis regardless of
their baseline characteristics. However, patients with lung metastasis-related finding at the initiation of lenvatinib treatment had a poorer prognosis among the lung metastasis group. It is important to consider not only the tumor size but also the presence of lung metastasis-related findings when initiating lenvatinib treatment for DTC with lung metastasis.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of Kanagawa Cancer Center (IRB approval no. 2022-4) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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