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Baseline Tumour Size as a Prognostic Factor for Radioiodine-refractory Differentiated Thyroid Cancer Treated With Lenvatinib

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Abstract. *Background/Aim: Lenvatinib is standard therapy for radioiodine-refractory differentiated thyroid cancer (RR-DTC), although the optimal timing for starting treatment is still controversial. The aim of this study was to evaluate the prognostic impact of baseline tumour size (BTS) in patients with RR-DTC treated with lenvatinib. Patients and Methods: Fifty-one RR-DTC patients who had at least one measurable lesion and treated with lenvatinib were retrospectively analysed. BTS was defined as the sum of the longest dimensions of all measurable target lesions. Results: Median progression-free survival (PFS) and overall survival (OS) in the larger BTS (≥42 mm) group were shorter than those in the smaller (<42 mm) group. This result was more significant in patients with fast-growing tumours. BTS was an independent prognostic factor for both PFS and OS. Conclusion: Starting lenvatinib at BTS <42 mm should be recommended to achieve good treatment outcomes in patients with RR-DTC.*

Lenvatinib is standard therapy for radioiodine-refractory differentiated thyroid cancer (RR-DTC). It is an oral multi-kinase inhibitor targeting vascular endothelial growth factor receptors (VEGFRs) 1-3, fibroblast growth factor receptors (FGFRs) 1-4, RET proto-oncogene, stem cell factor receptor (KIT), and platelet-derived growth factor receptor alpha (PDGFRα). The phase 3 SELECT (Study of E7080 "LEnvatinib" in differentiated Cancer of the Thyroid) trial demonstrated that lenvatinib has benefit for progression-free survival (PFS) in patients with RR-DTC (1).

The optimal timing to initiate multi-kinase inhibitors (MKIs) including lenvatinib and sorafenib has long been controversial because differentiated thyroid cancer has a slow-growing natural history, even if it becomes radioiodine-refractory (2, 3). Moreover, the adverse events of MKIs, such as fatigue, anorexia, and palmar-plantar erythrodysesthesia syndrome, can affect the patient's quality of life (4). Indeed, patients were required to have target lesions that had progressed according to the Response Evaluation Criteria in Solid Tumors (RECIST) within 13 or 14 months of enrolment in pivotal trials (1, 5). Therefore, lenvatinib should not be initiated simply because the target lesion is present.

In the SELECT trial, the baseline total target lesion diameter was 59.1 mm (range=15.1-331.2 mm) for patients who received lenvatinib, and smaller baseline tumour size (BTS) was associated with better PFS in the *post hoc* analysis [hazard ratio (HR)=0.61, 95% confidence interval (CI)=0.40-0.94, p=0.03] (6). Median overall survival (OS) of lenvatinib and placebo were 44.7 months and 33.1 months in patients with ≥10 mm lung metastasis, respectively (HR=0.63, 95% CI=0.47-0.85, p=0.0025). Despite the allowance of crossover after disease progression, median OS was shorter in patients with ≥10 mm lung metastasis, suggesting that the delay in starting lenvatinib in patients with ≥10 mm lung metastasis can affect OS. Indeed, median PFS (16.6 months) and OS (34.7 months) were relatively shorter in patients with ≥20 mm lung metastasis compared to patients with ≥10 mm lung metastasis (median PFS, 20.2 months; OS, 44.7 months) (7). In addition, the sum of the diameters of target lesions (>70 mm) and the maximum

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tumour diameter (>30 mm) were independent prognostic factors for PFS in a retrospective study (8). These results suggest that BTS can be a potential prognostic factor in patients with RR-DTC treated with lenvatinib. Herein, we performed an exploratory analysis to investigate the prognostic impact of BTS in patients with RR-DTC treated with lenvatinib.

Patients and Methods

We retrospectively reviewed the medical records of patients with RR-DTC who had undergone lenvatinib treatment at the Department of Medical Oncology of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (Tokyo, Japan) between January 2012 and September 2020. The patients received 24 mg lenvatinib (orally once daily). Treatment interruptions and dose reductions were permitted by the physicians according to the standard practice at our institute at the time. Treatment was continued until disease progression, unacceptable toxicity despite appropriate dose reduction and/or interruption, or the patient's refusal of treatment.

Treatment response was evaluated by computed tomography (CT) scans with thicknesses of 5.0 mm or less according to the RECIST criteria (ver. 1.1) (9). Measurable lesions were selected at a maximum of two lesions per organ and five lesions in total. The target lesions were required to be ≥10 mm on the longest diameter or ≥15 mm on the short axis if the lesion was a lymph node. BTS was defined as the sum of the longest dimensions of all measurable target lesions. Depth of response (DpR) was defined as the percentage (compared to baseline) of tumour shrinkage in the sum of the longitudinal diameters of target lesions at their smallest attained sizes.

The overall response rate (ORR) was defined as the percentage of patients with the best overall response of complete response (CR) or partial response (PR). The disease control rate (DCR) was the percentage of patients with a best overall response of CR, PR, or stable disease (SD). Patients without a measurable lesion were excluded from the analysis.

PFS was defined as the time from the first day of treatment to either the first objective evidence of disease progression, as confirmed by radiological images or obvious clinical manifestation of disease progression, or death from any cause. The OS was defined as the time from the first day of treatment to death by any cause.

Thyroglobulin doubling time (Tg-DT) and tumour volume doubling time (TV-DT) were calculated using the "Doubling Time, Doubling Rate & Progression Calculator" (Kuma Hospital, Hyogo, Japan) (10). EZR software (R ver. 4.0.3) (Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used for statistical analyses (11).

PFS and OS were estimated by the Kaplan–Meier method and were compared using a log-rank test. The survival results were expressed as the median value with a 95% CI. Mann–Whitney *U*-test was applied to analyse continuous data, while Fisher's exact test was used to compare categorical variables. The Cox hazard regression model was used to analyse prognostic factors. Spearman's rank correlation coefficient was used to evaluate the association between two variables.

This study was approved by the institutional review board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (2020-1032) and was conducted in accordance with the Helsinki Declaration of 1964 and later versions.

Results

Baseline characteristics. Of the 52 patients with RR-DTC treated with lenvatinib between January 2012 and September 2020, 51 patients who had at least one measurable lesion were enrolled in the analysis. The median age was 69 years (range=22-83 years), and 19 (37.3%) patients were men. The histological subtypes were papillary thyroid cancer (PTC) in 43 (90.5%) patients, follicular thyroid cancer (FTC) in seven (9.5%) patients, and poorly differentiated thyroid cancer (PDTC) in one patient. The mean cumulative dose of prior iodine-131 therapy was 179.0 mCi [standard deviation (SD)=130.3]. The median Tg-DT was 0.78 years (range=−5.99-21.88 years). A summary of the patient baseline characteristics is provided in Table I.

Baseline tumour size and tumour growth speed. Baseline tumour parameters are summarized in Table II. Metastatic sites were lung in 46 (90.2%), lymph node in 26 (51.0%), bone in 10 (19.6%), and liver in four (7.8%) patients. The median number of target lesions according to the RECIST was 2 (range=1-5). The number of target lung metastases was 72 in 40 patients, and the number of target lymph node metastases was 26 in 19 patients. The median BTS was 41.7 mm (range=15.4-119.9 mm), the sum of diameters of lung target lesions was 35.8 mm (range=10.1-58.5 mm), and sum of diameters of the lymph node target lesions was 21.8 mm (range=15.4-74.0 mm), respectively. The median TV-DT for all target lesions was 0.52 years (range=0.08-3.67 years) for 48 evaluable patients. The median maximum size of lung target lesions was 20.3 mm (range=10.1-44.5 mm), and the median maximum size of lymph node target lesions was 20.3 mm (range=15.4-50.0 mm).

Survival outcomes and baseline tumour size. At the data collection cut-off of December 24, 2020, the median follow-up time for all enrolled patients was 15.4 months (range=0.6-92.0 months). The ORR and DCR were 60.8% and 92.1%, respectively. Median PFS and OS were 20.3 months (95% CI=10.3-43.3) and 35.0 months (95% CI=19.1-NR), respectively.

The ORRs of the patients with larger (≥42 mm) and smaller (<42 mm) BTS were 54.5% and 74.1% (p=0.23), and the DCRs were 81.8% *vs.* 100.0% (p<0.05), respectively. Median PFS in patients with ≥42 mm BTS and <42 mm BTS was 10.6 months and 43.3 months (HR=2.26, 95% CI=1.01-5.07, p<0.05), respectively (Figure 1A). Median OS in patients with ≥42 mm BTS and <42 mm BTS was 19.1 months and 44.6 months (HR=2.88, 95% CI=1.15-7.20, p<0.03), respectively (Figure 1B). Both median PFS

Table I. *Patient characteristics*.

Characteristics	All N=51	BTS ≥42 mm N=24	BTS <42 mm N=27	*p*-Value
Age, years, median (range)	69 (22-83)	68 (47-83)	69 (22-80)	0.48
Gender, n (%)				0.02
Male	19 (37.3%)	13 (54.2%)	6 (22.2%)	
Female	32 (62.7%)	11 (45.8%)	21 (81.5%)	
ECOG PS, n (%)				0.57
0	20 (39.2%)	8 (33.3%)	12 (42.9%)	
1	31 (60.8%)	16 (66.7%)	15 (57.1%)	
Histological subtype, n (%)				1.00
Papillary thyroid cancer	43 (84.3%)	21 (87.5%)	22 (81.5%)	
Follicular thyroid cancer	7 (13.7%)	3 (12.5%)	4 (12.8%)	
Poorly differentiated cancer	1 (2.0%)	0 (0.0%)	1 (3.7%)	
Tumor-related symptom, n (%)	20 (39.2%)	10 (41.7%)	10 (37.0%)	0.78
Mean cumulative dose of iodine-131 therapy, mCi (SD)	179.0 (130.3)	187.3 (169.5)	171.1 (80.2)	0.68
Prior MKIs therapy, n (%)	7 (13.7%)	4 (16.7%)	3 (11.1%)	0.69
Neutrophil-to-lymphocyte ratio, median (range)	2.78 (1.29-24.36)	2.99 (1.35-24.36)	2.51 (1.29-6.95)	0.08
Thyroglobulin doubling time, years, median (range)	0.78 (–5.99-21.88)	0.56 (–5.99-4.07)	0.81 (–0.38-21.88)	0.29

BTS, Baseline tumor size; ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation, MKI, multi-kinase inhibitor.

Table II. *Baseline tumor parameters*.

Parameters	All N=51	BTS ≥42 mm N=24	BTS <42 mm N=27	*p*-Value
BTS (mm), median (range)	41.6 (15.4-119.9)	56.9 (42.0-119.9)	30.8 (15.4-41.7)	<0.001
No. of metastatic sites, median (range)	2 (1-4)	2 (1-3)	1 (1-4)	0.07
No. of measurable target lesions, median (range)	2 (1-5)	3 (1-5)	2 (1-2)	<0.001
Lung metastasis, n (%)	46 (90.2%)	23 (95.8%)	23 (85.2%)	0.35
≥10 mm	40 (78.4%)	22 (91.7%)	18 (66.7%)	0.04
10-20 mm	20 (39.2%)	9 (37.5%)	11 (40.7%)	1.00
≥20 mm	20 (39.2%)	13 (54.2%)	7 (25.9%)	0.05
Sum of diameters of lung metastasis (mm), median (range)	35.8 (10.1-58.5)	40.4 (11.2-58.5)	32.7 (10.1-41.7)	0.07
Maximum size of lung metastasis (mm), median (range)	20.3 (10.1-44.5)	21.0 (11.2-44.5)	17.7 (10.1-33.0)	0.25
Lymph node metastasis, n (%)	26 (51.0%)	14 (58.3%)	12 (44.4%)	0.40
Sum of diameters of LN metastasis (mm), median (range)	21.8 (15.4-74.0)	35.9 (16.5-74.0)	18.6 (15.4-49.0)	0.10
Maximum size of LN metastasis (mm), median (range)	20.3 (15.4-50.0)	21.8 (16.5-50.0)	18.6 (15.4-25.0)	0.15
Bone metastasis, n (%)	10 (19.6%)	5 (20.8%)	5 (18.5%)	1.00
Liver metastasis, n (%)	3 (5.9%)	1 (4.2%)	2 (7.4%)	1.00
Tumor volume doubling time, years, median (range)	0.52 (0.08-3.67)	0.52 (0.09-3.15)	0.51 (0.08-3.67)	0.92

BTS, Baseline tumor size; LN, lymph node.

and OS were shorter in patients with a larger BTS than those with a smaller BTS.

Interestingly, in patients with shorter TV-DT (defined as shorter than the median of 0.52 years), median PFS (7.7 months *vs*. NR, $p<0.01$) and OS (12.0 months *vs*. NR, $p=0.001$) were inferior in patients with a larger BTS than those with a smaller BTS (Figure 2A and B), whereas no significant difference was observed both in PFS (22.5 months *vs*. 15.1, $p=0.71$) and OS (NR *vs*. 44.6 months, $p=0.90$) in patients with a longer tumour volume doubling time (≥0.52 years) (Figure 2C and D).

In 46 patients with lung metastases, median PFS was not different between patients with lung metastasis of <20 mm (N=26) and ≥20 mm (N=20) (16.7 months *vs*. 10.3 months, HR=0.94, 95% CI=0.40-2.21, $p=0.89$). Median OS was also identical between patients with lung metastasis of <20 mm and ≥20 mm (27.6 months *vs*. NR, HR=0.85, 95% CI=0.33-2.15, $p=0.73$).

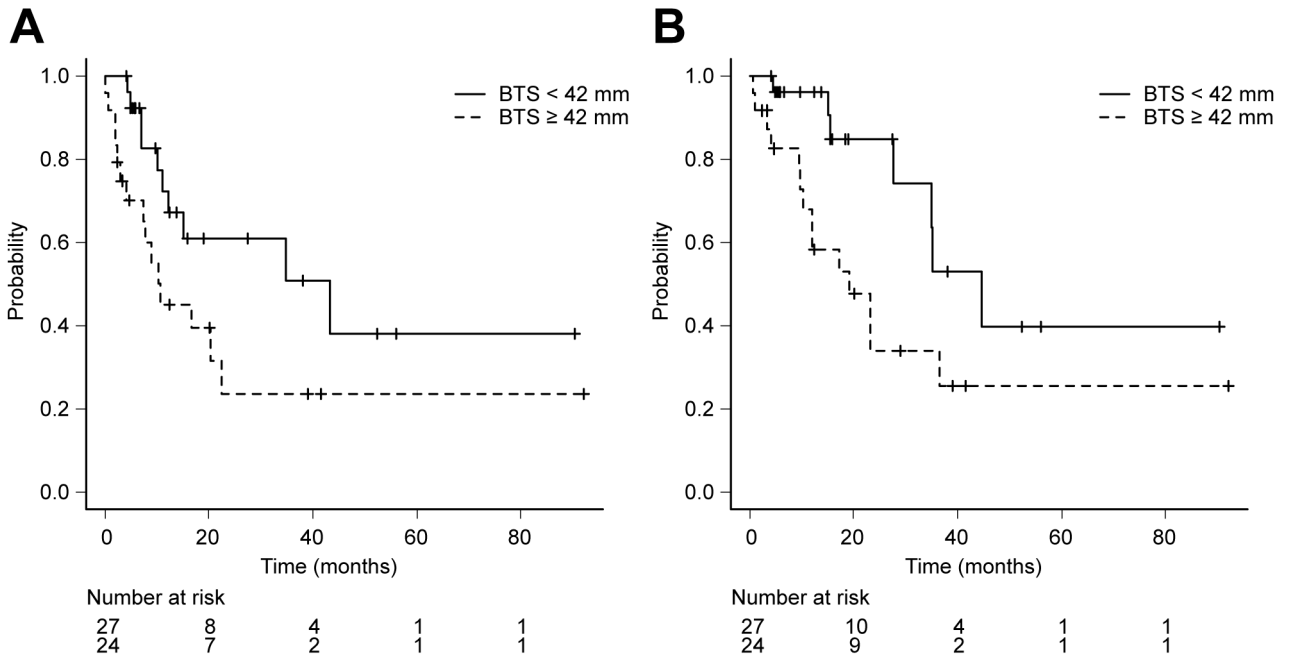

Figure 1. *Kaplan–Meier curves for progression-free survival (A) and overall survival (B) comparing patients with a larger BTS (≥42 mm) with those with a smaller BTS (<42 mm). BTS, Baseline tumour size.*

Baseline tumour size and the depth of response. Among the 51 patients, 49 patients underwent at least one CT evaluation after starting lenvatinib. In these 49 patients, the median DpR was 33.6% (range=−109.0.0-78.9), and there was no difference in DpR between patients with a larger BTS and a smaller BTS (32.7% *vs*. 34.9%, p=0.47). BTS was strongly correlated with the tumour size at the best response (r_s=0.85, p<0.001) (Figure 3A). The DpR was modestly associated with OS in all evaluable patients (r_s=0.43, p<0.003). Notably, this correlation was strongly observed in patients with a larger BTS (r_s=0.62, p<0.003), whereas no significant correlation was observed in patients with a smaller BTS (r_s=0.27, p=0.17) (Figure 3B).

Multivariate analysis for PFS and OS. BTS and the following six variables, which were reported as poor prognostic factors in previous studies, were included in the multivariate model: age (12), sex (13), bone metastasis (8, 14, 15), Tg-DT (16), neutrophil-to-lymphocyte ratio (17), and tumour-related symptoms (8, 18). Multivariate analysis revealed BTS as an independent predictive factor for PFS (HR=3.37, 95% CI=1.26-9.02, p<0.02) and OS (HR=4.14, 95% CI=1.42-12.11, p<0.01) (Table III).

Discussion

The efficacy of lenvatinib for patients with RR-DTC was demonstrated in the phase 3 SELECT trial and has been widely used in daily practice. However, the optimal timing and patient selection for initiating lenvatinib remain controversial because the OS benefit was not clear in the SELECT trial because of the crossover design (1). Our results showed that large BTS is associated with poor PFS and OS; thus, BTS can be a potential indicator to initiate lenvatinib treatment in RR-DTC patients. Notably, the difference in survival benefit between larger and smaller BTS patients diminished when the tumour growth speed was slow. This suggests that when tumours grow rapidly, lenvatinib should be started before the tumour becomes large.

Similar results that suggest radiographic tumour burden are associated with clinical outcomes in various cancers. Gross tumour volume has been associated with survival and recurrence in advanced nasopharyngeal cancer treated with definitive chemoradiotherapy (19). In advanced gastric cancer, large tumour size was an independent risk factor for lymph node metastasis and survival (20). In advanced non-small cell lung cancer treated with carboplatin/paclitaxel±bevacizumab, the baseline sum longest diameter was associated with survival in the *post hoc* analysis of the E4599 trial (21). For RR-DTC, BTS was associated with PFS in the SELECT trial (6). Our findings were consistent with these results, and we also identified an association between BTS and OS in patients with RR-DTC treated with lenvatinib.

In the *post hoc* analysis of the SELECT trial, median OS of patients with any size of lung metastasis was not

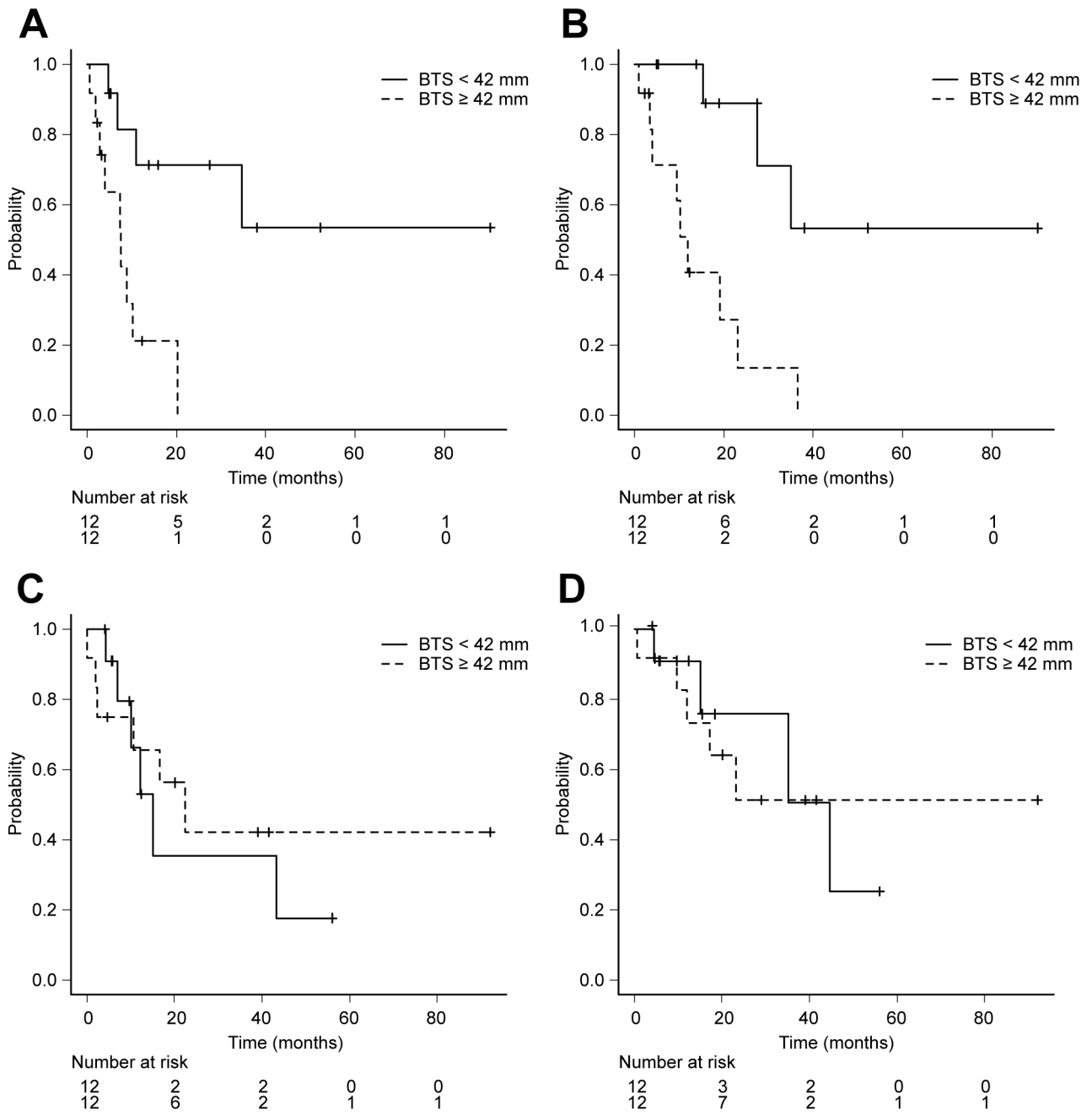

Figure 2. *Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) comparing patients with a larger BTS (≥42 mm) to those with a smaller BTS (<42 mm) according to TV-DT. PFS (A) and OS (B) in patients with fast-growing tumours (TV-DT <0.52 years), and PFS (C) and OS (D) in patients with slow-growing tumours (TV-DT ≥0.52 years). BTS, baseline tumour size; TV-DT, tumour volume doubling time.*

significantly different between the lenvatinib arm and the placebo arm (43.2 months *vs*. 34.0 months, HR=0.76, 95% CI=0.57-1.01, p=0.0549). However, for patients with ≥10 mm lung metastasis, median OS was longer in the lenvatinib arm compared with the placebo arm (44.7 months *vs*. 33.1 months, HR=0.63, 95% CI=0.47-0.85, p=0.0025) (7). Considering the crossover design of the SELECT trial, these results suggest that when lung metastasis grows up to 10 mm, a treatment delay of lenvatinib might ultimately affect the survival outcome. However, median PFS and OS were

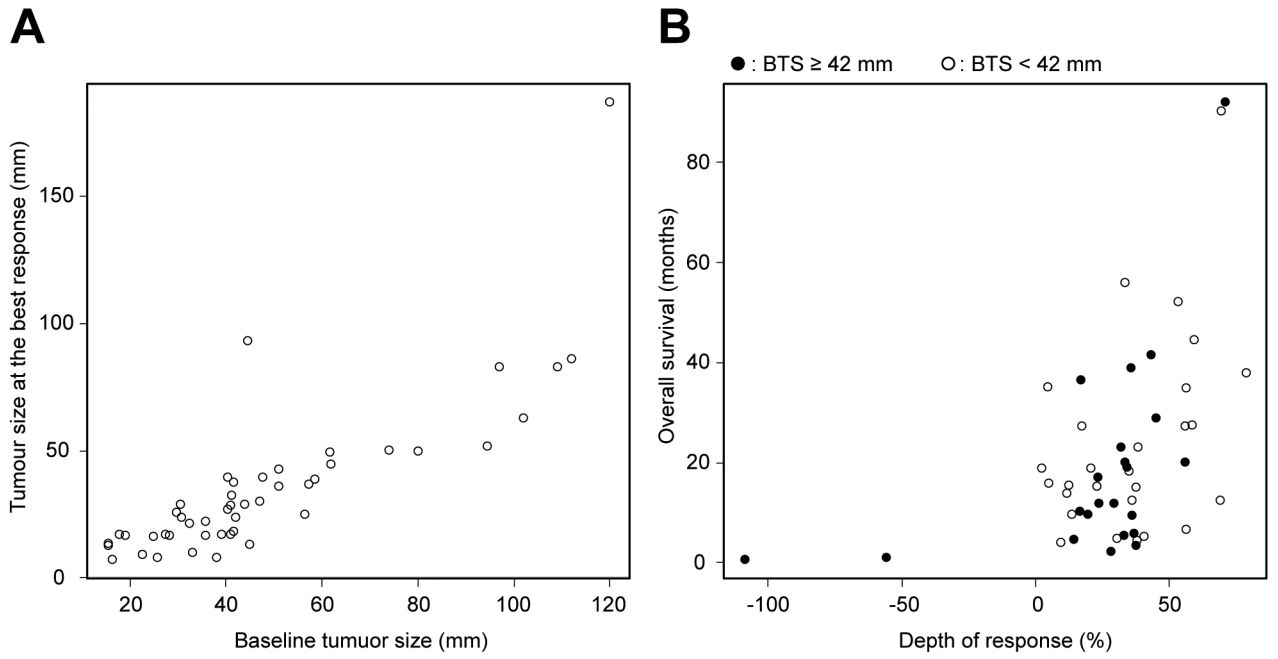

Figure 3. *Association between BTS and tumour size at the best tumour response (A) and between DpR and median overall survival (B) using Spearman's rank correlation coefficient. BTS, Baseline tumour size; DpR, depth of response.*

not different according to the size of lung metastasis (<20 mm *vs.* ≥20 mm) in the present study. Despite the imbalance in the number of patients, we performed an additional analysis to compare the survival outcomes between patients with <10 mm lung metastasis (n=6) and ≥10 mm (n=40). Both PFS (17.7 months *vs.* 22.5 months, p=0.77) and OS (23.1 months *vs.* 27.6 months, p=0.63) were not different between the two groups. The discordance in the results between the SELECT trial and the present study might be explained by the small patient number and the imbalance in the patients enrolled in our study. Another possible explanation is that metastases other than lung metastasis can affect survival outcomes and offset the impact of the size of the lung metastasis. The tumour size of all target lesions rather than lung metastasis might be better a prognostic indicator for RR-DTC treated with lenvatinib.

In the present study, BTS was strongly correlated with the tumour size at the best tumour response, although the median DpR also was not different between patients with a larger BTS and a smaller BTS (32.6% *vs.* 34.9%, p=0.47). Our findings also demonstrated the relationship between DpR and OS. Notably, the association between DpR and OS was evident only in patients with a larger BTS. This suggests that the clinical impact of the DpR might be affected by tumour burden, and a deeper tumour response may be required to prolong OS of RR-DTC patients with a larger BTS. Our results suggest the difficulty of achieving an adequate tumour response to prolong OS in patients with larger tumours, because the ORR and the median DpR were not different between larger and smaller BTS.

The molecular and biological mechanisms for the association between tumour size and poor survival outcomes are unclear. Several studies indicated that larger tumours may have a poor blood supply and elevated interstitial pressure and hypoxia (22, 23). Indeed, hypoxia is reported to mediate resistance to antiangiogenic agents such as tyrosine kinase inhibitors in several solid tumours (24-27). When tumour cells are exposed to hypoxia, the expression of hypoxia-inducible factor 1 alpha (HIF-1α) causes up-regulation of alternative angiogenic factors or inflammatory cytokines, such as basic fibroblast growth factor (bFGF) and interleukin 8 (IL-8) (28, 29). HIF-1α can also affect the derivation of bone marrow-derived cells, which mediate angiogenesis and tumour invasion (30, 31). In several differentiated thyroid cancer cell lines, HIF-1α overexpression followed by prolonged hypoxia leads epithelial-to-mesenchymal transition, resulting in tumour invasion and migration (32). Moreover, it is reported that tumour hypoxia is associated with and the immune response, further associated with poor prognosis in patients with colorectal cancer (33). As well as other malignancies, tumour immunity is associated with thyroid cancers (34). Regulatory T cell (T_{reg}) is well-known to suppress the immune response and can promote tumour progression. Indeed, it is reported that T_{reg} cells are present in invasive thyroid cancer (pT4),

Table III. *Multivariate analysis for progression-free survival and overall survival.*

	Progression-free survival			Overall survival		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age						
<65 years	Reference			Reference		
≥65 years	0.99	0.39-2.48	0.98	1.27	0.44-3.63	0.65
Gender						
Male	Reference			Reference		
Female	0.34	0.10-1.19	0.09	0.31	0.09-1.11	0.07
Bone metastasis						
No	Reference			Reference		
Yes	1.25	0.37-4.27	0.72	0.96	0.28-3.30	0.95
Thyroglobulin doubling time						
<1 years	Reference			Reference		
≥1 years	0.37	0.12-1.13	0.08	0.37	0.11-1.29	0.12
Neutrophil-to-lymphocyte ratio						
<3	Reference			Reference		
≥3	0.63	0.22-1.80	0.39	0.58	0.18-1.85	0.36
Tumor-related symptom						
No	Reference			Reference		
Yes	0.98	0.32-3.01	0.98	1.98	0.66-5.91	0.22
Baseline tumor size						
<42 mm	Reference			Reference		
≥42 mm	3.37	1.26-9.02	<0.02	4.14	1.42-12.11	<0.01

HR, Hazard ratio; CI, confidence interval.

suggesting that the immune-suppressive microenvironment can promote tumour progression in thyroid cancers (35). These tumour microenvironments can provide a possible explanation for the poor treatment outcomes of lenvatinib in RR-DTC patients with larger BTS.

The present study has several limitations. First, we should consider the retrospective nature and small sample size of this study. Because of the retrospective analysis of the daily practice, the treatment protocol, such as the timing of starting lenvatinib and the interval of CT evaluation, was not standardized. The CT images were evaluated by only a single investigator. Although we set the cutoff of BTS at 42 mm according to the median value of our cohort, the optimal cutoff value has not been established. The cutoff value of BTS was 70 mm in a retrospective exploratory study (8), whereas it was set at 59.1 mm according to the median value in the SELECT trial (6). Our findings defining a cutoff value of 42 mm for BTS, which is smaller than previous reports, suggest that lenvatinib should be initiated earlier than previously reported, before tumours grow. As tumour evaluation is based on the RECIST, our results cannot be applied to patients without measurable lesions. For example, patients with diffuse small lung metastases, diffuse bone metastases, and diffuse pleural disseminations can have massive tumour volumes but are not measurable by the RECIST, yet these patients frequently demonstrate poor prognosis.

Despite these limitations, the strength of the present study is that, for the first time, we investigated the prognostic impact of BTS according to tumour growth speed. The findings can help physicians decide the initiation of lenvatinib during active surveillance for metastatic disease. Considering the adverse events, lenvatinib should not be initiated when the patients are solely radioiodine-refractory. When patients have larger tumours, physicians should consider starting lenvatinib regardless of the tumour growth speed. Moreover, for patients with fast-growing but small tumours, lenvatinib should be initiated before the tumours become larger, not only because of the poor survival outcomes but also of the increased risk of bleeding and fistula which can be life-threatening adverse events (36).

In conclusion, we identified that larger tumours at baseline are associated with poor PFS and OS in patients with RR-DTC patients treated with lenvatinib. Our findings also suggest that the impact of BTS is remarkable in patients with fast-growing tumours. Tumour size and tumour growth speed should be carefully evaluated during active surveillance, and lenvatinib should be initiated when a tumour grows rapidly with a large tumour volume (BTS ≥42 mm). Although a further prospective study is required to validate our findings, we determined that BTS is a significant predictor of PFS and OS and can be an indicator to initiate lenvatinib in patients with RR-DTC.

Conflicts of Interest

NF, KT, and JT received personal fees from Eisai outside the submitted work. YS reports personal fees from Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb Company, MSD K.K., and Taiho Pharmaceutical Co., Ltd. outside the submitted work. ST reports grants and personal fees from Ono Pharmaceuticals and Bristol-Myers Squibb during the conduct of the study, and grants and personal fees from MSD, AstraZeneca, Chugai, and Bayer outside the submitted work. The Authors report no other conflicts of interest in this work.

Authors' Contributions

Conception and design: N Fukuda. Acquisition of data: N Fukuda. Analysis and interpretation of data: N Fukuda. Writing the manuscript: N Fukuda. Review, and/or revision of the manuscript: All Authors.

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