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Head and Neck Cancers

Clinicopathological Features Predict Outcomes in Patients with Radioiodine-Refractory Differentiated Thyroid Cancer Treated with Sorafenib: A Real-World Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Radioiodine-refractory differentiated thyroid cancer • Clinicopathological features • Response • Progression-free survival • Overall survival • Sorafenib

Abstract

Background. Because beneficial response and progression-free survival (PFS) were achieved by well-designed clinical trials with tyrosine kinase inhibitors (TKIs) in patients with progressive radioiodine-refractory differentiated thyroid cancer (RR-DTC), the overall survival (OS) and improvement of therapeutic outcomes in the real world have been anticipated.

Subjects, Materials, and Methods. This prospective, single-center, real-world study assessed the predictive significance of clinicopathological features on disease control rate (DCR), objective response rate (ORR), PFS, and OS in a cohort of 72 patients with progressive RR-DTC treated with sorafenib at an initial dose of 200 mg twice daily.

Results. Disease control, objective response, and biochemical effectiveness were achieved in 73.3%, 21.7%, and 77.9% of patients, respectively. The median PFS and OS were 17.6 and 28.9 months, respectively. Multivariate analyses showed that hand-foot syndrome (HFS) was an independent predictor for better DCR and ORR, and ^{131}I-avidity for higher ORR. In univariate analyses, longer PFS and OS were observed in patients with Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2, pathologically well DTC, lung-only metastasis, absence of bone metastasis, biochemically noneffective response, HFS, or radiological disease control. In multivariate analyses, only well DTC and ECOG PS ≤2 remained as independent prognostic factors for more favorable PFS and OS, respectively, whereas the absence of bone metastasis and biochemically noneffective response independently predicted superior PFS and OS.

Conclusion. This study demonstrated that clinicopathological features might play a vital role in predicting therapeutic outcomes in patients with progressive RR-DTC treated with sorafenib, warranting further optimization of candidates for TKIs. ***The Oncologist*** 2020;25:e668–e678

Implications for Practice: This prospective, single-center, real-world study was designed to investigate the significance of clinicopathological features in predicting response, progression-free survival, and overall survival in patients with progressive radioiodine-refractory differentiated thyroid cancer (DTC) treated with sorafenib. Multivariate analyses showed that hand-foot syndrome was an independent predictor for better response. Meanwhile, well DTC, Eastern Cooperative Oncology Group performance status ≤2, biochemically noneffective response, and the absence of bone metastasis were independent prognostic factors for more favorable survival. This study demonstrated that clinicopathological features might play a vital role in predicting outcomes in sorafenib-treated patients with radioiodine-refractory DTC, warranting optimization of indications.

Introduction

Thyroid cancer is the most prevalent endocrine malignancy. Approximately 567,000 new cases worldwide were identified in 2018 [1]. The estimated incidence rate of thyroid cancer in China has dramatically increased over the last decades, achieving around 90,000 new cases in 2015 [2]. Around 96% of thyroid cancers originate from follicular cells, and of these, 99% are differentiated thyroid cancer (DTC). DTCs are categorized into well DTC (papillary thyroid cancer [PTC], follicular thyroid cancer [FTC], and Hürthle cell cancer) and poorly DTC [3, 4].

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Optimistic prognosis of DTC is commonly achieved because of its indolent nature and adequate management strategies, such as surgery, radioiodine (^{131}I) treatment, and levothyroxine therapy. However, persistent/recurrent or metastatic DTC, which is inoperable or refractory to ^{131}I therapy and/or tumor progression despite thyroid-stimulating hormone (TSH) suppression, has become the main cause of disease-specific death with a 10-year survival rate as low as 10% [5]. Therapeutic options have been historically limited in patients with radioiodine-refractory DTC (RR-DTC).

In the last decade, tyrosine kinase inhibitors (TKIs) such as sorafenib and lenvatinib have been approved by the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of progressive RR-DTC based on phase III clinical trials [6, 7]. Sorafenib, an orally active TKI that targets BRAF, VEGFR1-2, and RET, was the first TKI available worldwide for the treatment of patients with progressive RR-DTC [8].

However, many studies including clinical trials have only reported progression-free survival (PFS) in patients with progressive RR-DTC with Eastern Cooperative Oncology Group performance status (ECOG PS) scores of 0-2, and the efficacy of sorafenib remains unknown in patients with a poor ECOG PS (>2) [7, 9, 10]. Thus, real-world studies are strongly needed to delineate the full view of clinical setting. Furthermore, available data regarding median PFS varied widely, ranging from 9 to 24 months [10–15], and enormous differences in objective response rate (ORR), ranging from 12.2% to 31%, were also observed in previous studies [7, 9]. The above discrepancies may be attributed to varying clinicopathological demographic characteristics among studies. Moreover, data on OS are quite rare, shading the landscape of TKIs used in this specific field [9, 16].

Similar to other TKIs, it is worth noting that the overall therapeutic benefits of sorafenib were not as ideal as expected, although the phase III clinical trial gave positive PFS results (sorafenib compared with placebo, 10.8 vs. 5.8 months, $p < .0001$). Furthermore, comparisons of PFS and response were merely performed between sorafenib-treated subjects and placebo-treated subjects. However, direct comparisons of therapeutic efficacy between subgroups with and without specific clinicopathological features were lacking in the sorafenib-treated group [7]. Although a few sporadic reports have attempted to define the actual role of a few clinicopathological characteristics in a clinical context, relatively small sample sizes and short follow-up times severely limited their impact [10, 16]. Therefore, this dedicated prospective, single-center, real-world study was performed to investigate the significance of clinicopathological features in predicting response, PFS, and OS in patients with progressive RR-DTC treated with sorafenib, in order to further optimize indications and ameliorate clinical practice.

Subjects, Materials, and Methods

Patients

Patients with progressive locally advanced and/or metastatic RR-DTC were prospectively enrolled from August 2009 through October 2016 using the criteria recently described by our team as follows: (I) foci never concentrated ^{131}I, that is, absence of ^{131}I-avidity from the beginning; (II) despite previous evidence of ^{131}I concentration, the foci lost the ability to be ^{131}I-avid; (III) concentration presented in some foci but not in others despite the significant concentration of ^{131}I; or (IV) ^{131}I-avid metastasis progressed within 1 year after ^{131}I therapy [17]. The absence (criterion I) and presence (criteria II–IV) of ^{131}I-avidity were defined based on the findings of a post-therapeutic ^{131}I scan. All patients who were enrolled had evidence of disease progression according to RECIST version 1.1 within 12 months prior to initiation of treatment despite taking enough thyroid hormone to maintain serum TSH under 0.1 mIU/L [18]. Premenopausal women were required to have negative pregnancy tests, and all patients of childbearing potential were required to use contraception. Patients were treated independently from ECOG PS, systematic chemotherapy, and life expectancy.

The ethics board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital approved the protocol prior to the beginning of the study. All subjects gave written informed consent for participation in the study.

Study Design

This was a prospective, single-center, real-world study. The objective of this study was to determine the predictive significance of clinicopathological features on outcomes in patients with RR-DTC treated with sorafenib. As previously reported by our group, sorafenib was initially administered at a dose of 200 mg orally twice a day until it was discontinued because of disease progression, uncontrollable side effects, or death or at the patient's request [15, 19, 20]. Screening evaluations, including medical history, demography, review of prior treatment, physical examination, baseline imaging, and laboratory evaluations, were completed within 1 week before the start of sorafenib administration. After beginning treatment, patients were observed at intervals of 4-8 weeks. At each visit, a history and physical examination were performed, and levels of TSH, thyroglobulin (Tg), and anti-Tg antibody (TgAb) were tested. Safety and tolerability were also monitored. Adverse event (AE) severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). The radiological response was assessed every 2–3 months.

Radiographic Assessments

Radiographic assessments were performed by competent radiologists using computed tomography (CT), magnetic resonance imaging, or positron emission tomography combined with diagnostic CT (PET/CT). The radiological response was defined according to RECIST 1.1 as follows: complete response (CR): disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm; partial response (PR): ≥30% decrease in the sum of target lesions size; progressive disease (PD): ≥20% increase in the sum of target lesions size or new metastatic lesion; stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. SD and PR were categorized as disease control, whereas CR and PR were collectively defined as objective response [18]. Patients without target lesions were excluded from radiographic response analysis but were included in the survival analysis.

Biochemical Evaluations

Serum TSH, Tg, and TgAb levels were measured by electrochemiluminescence immunoassay on a Cobas analyzer (Roche Diagnostics Gmbh, Roche Ltd., Basel, Switzerland). In terms of biochemical response, a decrease of at least 25% in Tg levels was considered effective, an increase of at least 25% was considered ineffective, and changes in Tg <25% were classified as stable [16]. Tg change percentage = $(Tg_{min} - Tg_{baseline})/Tg_{baseline}$. $Tg_{baseline}$ and Tg_{min} referred to the serum Tg level just before sorafenib treatment and the lowest serum Tg level during the treatment, respectively. Patients were excluded from the analysis of biochemical response when serum TgAb was positive (>100 IU/mL), which was reported by our team [21]. Effective and stable responses were collectively defined as a noneffective response.

Statistical Analyses

All analyses were conducted using SPSS version 20.0 (IBM Corp., Armonk, NY). Descriptive statistics included median and the minimum and maximum of continuous factors and scores. In the case of categorical variables, numbers and percentages were compared using the chi-square analysis. Multivariate logistic regression was used to identify the association between response and clinicopathological features. The cumulative probability of PFS (defined as the time from starting sorafenib treatment to progression or death, whichever occurred first) and OS (defined as the time from the first dose of sorafenib to death from any cause) was calculated using Kaplan-Meier survival estimates. A log-rank test was used to test for the difference between time-to-event curves. Cox proportional hazards modeling was used to estimate the risk of disease persistence/progression and death from any cause, after adjusting for age and all other factors that had been proved to be associated with PFS and OS in multivariate analyses. Two-tailed probabilities were reported, and a p value <.05 was used to define nominal statistical significance.

Results

Baseline Characteristics

The baseline clinicopathological characteristics of all 72 enrolled patients are summarized in supplemental online Table 1. The median age was 56.9 years (range, 18–79 years). The ratio of females to males was nearly 2:1. An ECOG PS >2 was observed in 13 (18%) patients. More than 70% of patients were pathologically diagnosed as PTC, and 12.5% were diagnosed as poorly DTC. Except for 6 (8.3%) patients with locally advanced disease, lung (88.9%) and bone (31.9%) were most frequently involved organs by metastasis of RR-DTC, and lung-only metastasis presented in 27 (37.5%) patients. The median duration between DTC diagnosis and sorafenib administration was 6.5 years (range, 0.1–42.9 years).

Before the initiation of sorafenib treatment, all patients had undergone ^{131}I therapy with a median cumulative activity of 11.1 GBq (range, 3.7–46.3 GBq). In detail, the median cumulative activities in ^{131}I-avid group and ^{131}I-nonavid group were 20.4 GBq (range, 3.7–46.3 GBq) and 7.4 GBq (range, 3.7–22.2 GBq), respectively. Besides, 9 (12.5%) patients had undergone external beam radiation therapy (2 for bone lesion, 1 for brain lesion, and 6 for neck lesion), 2 (2.8%) patients had received systemic chemotherapy, and 28 (38.9%) patients had experienced resection of metastatic tumor.

The absence of ^{131}I-avidity from the beginning occurred in nearly half of patients (52.8%). None of the subjects had received other TKIs prior to the sorafenib treatment. Median duration of sorafenib treatment was 6.5 months (range, 0.8–94.5 months), and median follow-up duration from sorafenib administration to censoring or death was 25.1 months (range, 0.8–113 months).

Table 1. The association between clinicopathological features and radiological response to sorafenib in patients with radioiodine-refractory differentiated thyroid cancer (n = 60)

Variable	DCR, %	p value	ORR, %	p value
Gender		.603		.991
Female	75.7		21.6	
Male	69.6		21.7	
Age, years		.836		.658
≥55	72.5		25	
<55	75.0		20	
ECOG PS		.368		.965
≤2	76.5		21.6	
>2	55.6		22.2	
Differentiation status		.029		.403
Well	77.8		24.1	
Poorly	33.3		0	
Pathological subtype		.357		.769
PTC	80.9		23.4	
FTC	57.1		28.6	
Lung metastasis		.498		.924
Yes	74.5		21.8	
No	60.0		20.0	
Lung-only metastasis		.084		.035
Yes	87.5		35.7	
No	63.9		11.1	
Bone metastasis		.041		.338
Yes	55.6		11.1	
No	81.0		26.2	
Locally advanced		.793		.219
Yes	66.7		0	
No	73.7		22.8	
Presence of ^{131}I-avidity		.757		.014
Yes	71.4		35.7	
No	75.0		9.6	
Hand-foot syndrome		.002		.021
Yes	92.6		37.0	
No	56.7		9.1	

Abbreviations: DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; FTC, follicular thyroid cancer; ORR, objective response rate; PTC, papillary thyroid cancer.

Table 2. Univariate analyses of potential prognostic factors associating with the survival of patients with radioiodine-refractory differentiated thyroid cancer treated with sorafenib

Variable	*n*	PFS, months	*p* value	*n*	OS, months	*p* value
Gender			.0541			.3148
Female	46	20.27		22	55.87	
Male	26	10.73		38	22.77	
Age, years			.1701			.0946
≥55	48	10.73		41	22.50	
<55	24	22.77		19	NR	
ECOG PS			.002			<.0001
≤2	59	20.27		47	79.80	
>2	13	6.07		13	6.67	
Differentiation status			.0024			.0101
Well	63	18.40		52	50.80	
Poorly	9	3.63		8	13.10	
Pathological subtype			.1659			.2857
PTC	56	20.30		47	55.90	
FTC	7	6.07		5	13.00	
Lung metastasis			.7053			.1396
Yes	64	17.60		53	36.23	
No	8	6.50		7	21.23	
Lung-only metastasis			.0016			.0005
Yes	27	39.90		21	NR	
No	45	8.37		39	21.23	
Bone metastasis			<.0001			<.0001
Yes	23	6.67		20	10.27	
No	49	28.57		40	NR	
Locally advanced			.4770			.4986
Yes	6	16.73		4	21.23	
No	66	21.23		56	28.93	
Presence of ^{131}I-avidity			.4928			.0623
Yes	34	9.23		30	15.07	
No	38	22.77		30	79.80	
Biochemical response			.0047			.0001
Noneffective	65	17.83		54	55.87	
Ineffective	3	3.40		2	3.90	
Hand-foot syndrome			.0313			.0412
Yes	31	20.27		23	84.73	
No	41	7.10		37	21.23	
Disease control			<.0001			.0001
PR + SD	44	28.93		34	NR	
PD	16	2.83		14	6.47	
Objective response			.1965			.1473
PR	13	39.90		13	NR	
SD + PD	47	11.50		35	28.93	
Salvage treatment						.0410
Yes	—	—		12	NR	
No	—	—		60	28.93	

Abbreviations: —, no data; ECOG PS, Eastern Cooperative Oncology Group performance status; FTC, follicular thyroid cancer; NR, not reached; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PTC, papillary thyroid cancer; SD, stable disease.

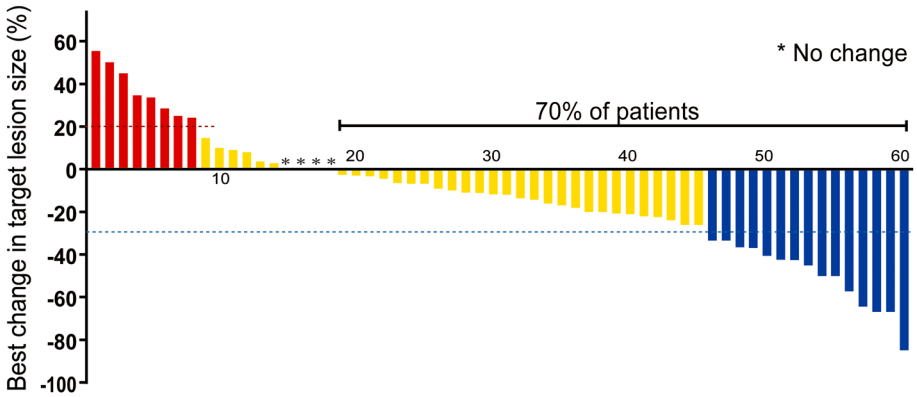


Figure 1. Best changes in the sum of the largest diameter of target lesions from baseline (n = 60).

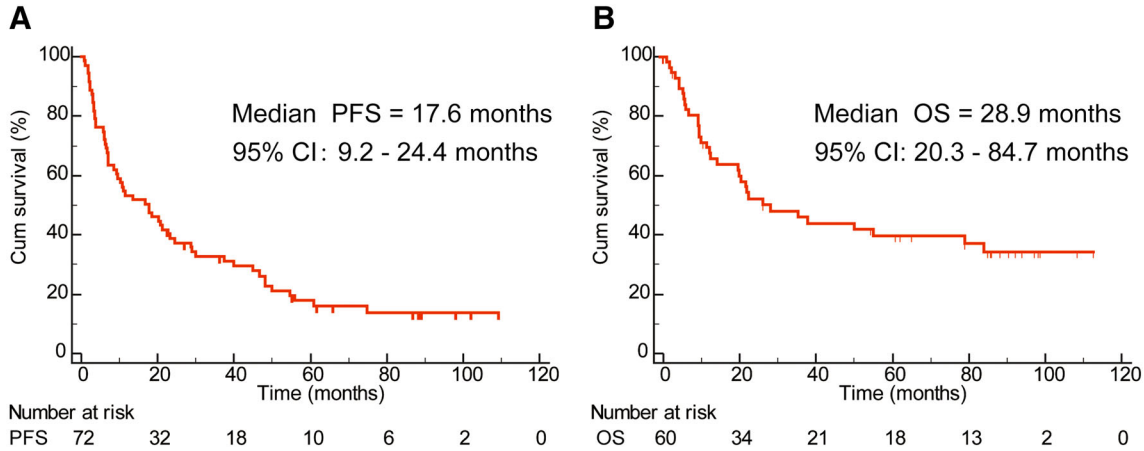


Figure 2. Kaplan-Meier curves of survival in patients with progressive radioiodine-refractory differentiated thyroid cancer treated with sorafenib. **(A):** PFS (n = 72). **(B):** OS (n = 60).
Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Safety

AEs were reported in 53 (73.6%) patients receiving sorafenib treatment (supplemental online Table 2). These events were predominantly grades 1 or 2, and severe AEs (grades 3 or 4) occurred in only 12 (16.7%) patients. The most frequent AE was hand-foot syndrome (HFS) (43.1%), followed by alopecia (25.0%), diarrhea (22.2%), weight loss (16.7%), fatigue (15.2%), rash or desquamation (11.1%), hypertension (9.7%), and oral mucositis (8.3%), etc. No patient died of probable therapy-associated severe AEs. The mean daily dose of sorafenib was 368 $\pm$ 71 mg. Drug interruptions, reductions, and withdrawals due to AEs occurred in 3 (4.2%), 11 (15.2%), and 1 (1.4%) patients, respectively.

Clinicopathological Features Predict Response

Radiological Response

After exclusion of 2 patients who died before the first radiological assessment and 10 patients without target lesion, the remaining 60 (83.3%) patients were eligible for the assessment of radiological response. There were no CRs. The total proportion of PR was 21.7% (n = 13), and 31 (51.7%) patients showed SD. Best changes in the sum of the largest diameter of target lesions from baseline are illustrated in Figure 1.

Univariate analyses of the association between clinicopathological features and radiological responses are shown in Table 1. There were no significant differences in DCRs and ORRs regarding age, gender, ECOG PS, lung metastasis, or locally advanced disease. Notably, DCR was more favorable in patients with well DTC than in those with poorly DTC (p = .029), although no significant difference was found between PTC and FTC (p = .357). DCR was worse in patients with bone metastasis (p = .041); however, ORRs were better in subjects with lung-only metastasis and patients with ^{131}I-avid lesions (p = .035 and .014, respectively). Interestingly, HFS occurred in 43.1% of patients, who had better DCR and ORR than those without HFS (p = .002 and .021, respectively).

Multivariate analyses revealed that HFS was independently associated with better DCR and ORR (p = .009 and .008, respectively). Besides, ^{131}I-avidity was an independent predictor associated with better ORR (p = .011). Other factors, including gender, age, ECOG PS, differentiation status of DTC, pathological subtype of well DTC, bone metastasis, lung metastasis, lung-only metastasis, and locally advanced, could not independently predict either DCR or ORR (p > .05).

Biochemical Response

Four (5.9%) patients were excluded from the analysis of change in Tg level because of positive TgAb. Of the remaining

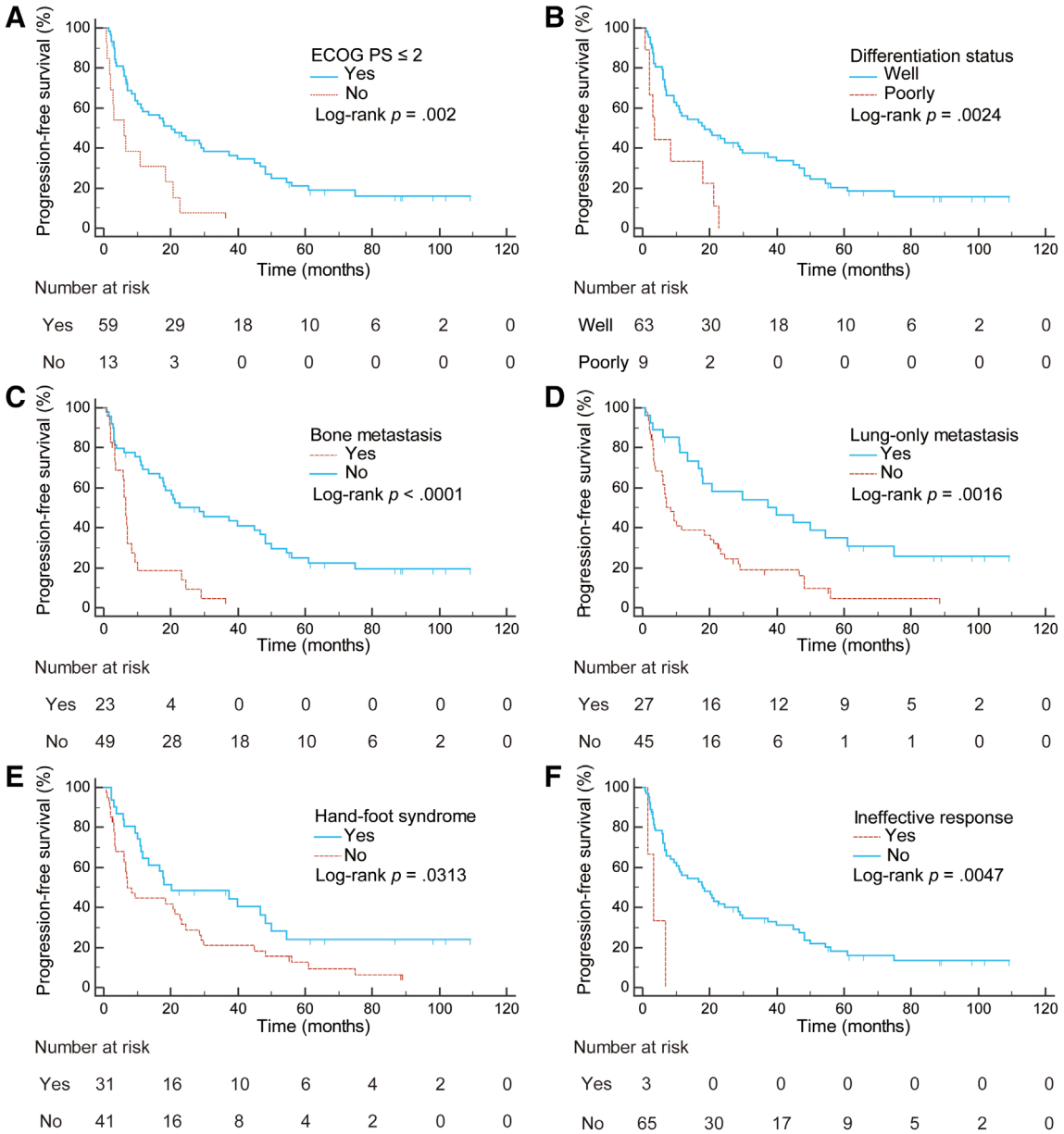


Figure 3. Kaplan-Meier estimates of progression-free survival according to clinicopathological features. **(A):** ECOG PS ≤2 (yes or no). **(B):** Differentiation status of differentiated thyroid cancer (well or poorly). **(C):** Bone metastasis (yes or no). **(D):** Lung-only metastasis (yes or no). **(E):** Hand-foot syndrome (yes or no). **(F):** Biochemically ineffective response (yes or no).
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

68 patients, most (77.9%) had an effective biochemical response, and the Tg levels in 17.6% (n = 12) patients were stable. A few patients (4.4%) had a biochemically ineffective response. The mean serum Tg level decreased significantly, reaching the nadir within about 12.2 weeks after sorafenib administration.

No relationship between biochemical response and the aforementioned clinicopathological features was found in either univariate analyses or multivariate analyses (p > .05).

Clinicopathological Features Predict Survival

All patients were enrolled in the analysis of PFS. Twelve patients were ruled out in the analysis of OS as a result of the interference of salvage treatments (apatinib in 8, anlotinib in 3, and sunitinib in 1). Kaplan-Meier survival estimates of PFS and OS in the population are shown in Figure 2. A median PFS of 17.6 months (95% confidence interval [CI]: 9.2–-24.4 months) and a median OS of 28.9 months (95% CI: 20.4–-84.7 months) were achieved in our single-arm study, which was coupled with the following prognostic analyses.

Univariate Analyses

As listed in Table 2, no significant differences in PFS and OS were identified regarding age, gender, the presence of lung metastases, locally advanced disease, and ^{131}I-avidity. Moreover, there were no significant differences in PFS and OS between patients with PTC and FTC.

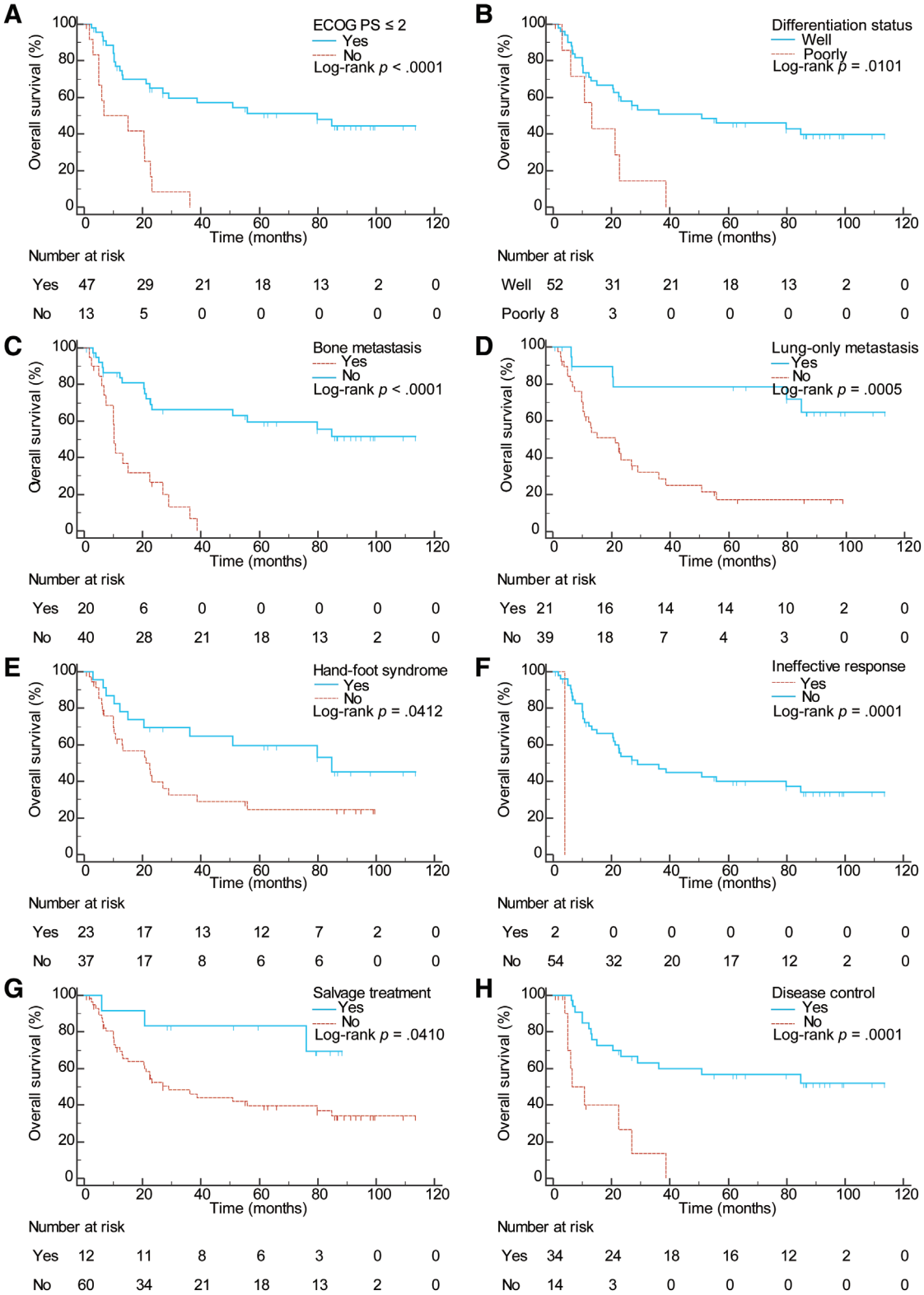
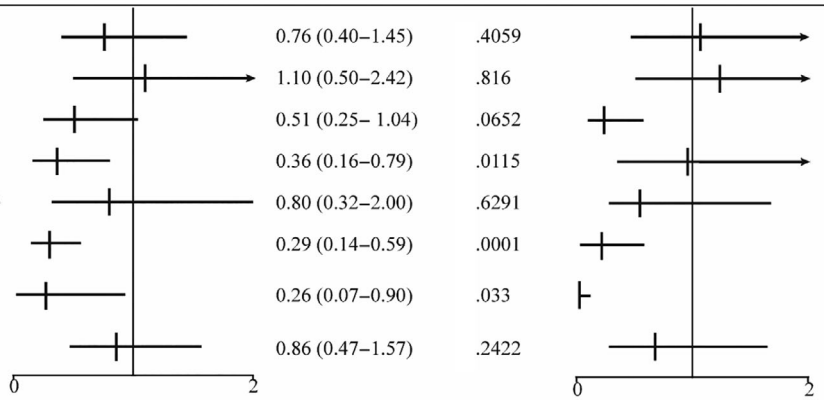


Figure 4. Kaplan-Meier estimates of overall survival regarding clinicopathological features. **(A):** ECOG PS ≤2 (yes or no). **(B):** Differentiation status of differentiated thyroid cancer (well or poorly). **(C):** Bone metastasis (yes or no). **(D):** Lung-only metastasis (yes or no). **(E):** Hand-foot syndrome (yes or no). **(F):** Biochemically ineffective response (yes or no). **(G):** Salvage treatment (yes or no). **(H):** Disease control (yes or no).
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

Kaplan-Meier survival estimates of PFS and OS with significant differences according to clinicopathological characteristics are shown in Figures 3 and 4, respectively. PFS and OS were found to be strikingly associated with baseline ECOG PS (p = .002 and <.0001, respectively). Patients with well DTC had better PFS and OS than those with poorly DTC (p = .0024 and

Table 3. Multivariate analyses of potential prognostic factors for progression-free survival and overall survival in patients with radioiodine-refractory differentiated thyroid cancer treated with sorafenib using Cox's proportional hazards model

Variable	Progression-free survival ($n = 68$)		Overall survival ($n = 56$)	
	HR (95% CI)	p valve	HR (95% CI)	p valve
Female	0.76 (0.40–1.45)	.4059	1.07 (0.47–2.41)	.8716
Age ≥ 55 y	1.10 (0.50–2.42)	.816	1.24 (0.51–3.05)	.6301
ECOG PS ≤ 2	0.51 (0.25– 1.04)	.0652	0.24 (0.10– 0.58)	.0017
Well DTC	0.36 (0.16–0.79)	.0115	0.94 (0.34–2.56)	.9105
Lung-only metastasis	0.80 (0.32–2.00)	.6291	0.55 (0.18–1.68)	.2909
No bone metastasis	0.29 (0.14–0.59)	.0001	0.23 (0.09–0.60)	.0022
Biochemically non-ineffective response	0.26 (0.07–0.90)	.033	0.01 (0.007–0.14)	.0005
Hand-foot syndrome	0.86 (0.47–1.57)	.2422	0.68 (0.28–1.65)	.3952



The arrow indicates that the value is out of range.
Abbreviations: CI, confidence interval; DTC, differentiated thyroid cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; y, years.

.0101, respectively). Significant differences in PFS and OS were found between subjects with and without bone metastases (p < .0001 and < .0001, respectively). Better PFS and OS were found in patients with lung-only metastasis compared with other patients (p = .0016 and .0005, respectively). Patients with HFS had more favorable PFS and OS compared with others (p = .0313 and .0412, respectively). Compared with patients with PD and patients without salvage treatment, superior OSs were noticed in patients with disease control and salvage treatment (p = .0001 and .0410, respectively, both median OSs had not reached yet). Notably, patients with biochemically nonineffective response had much better prognoses than those showing biochemically ineffective response (median PFS, 17.83 vs. 3.40 months, p = .0047; median OS, 55.87 vs. 3.90 months, p = .0001; Table 2).

Multivariate Analyses

In the multivariate analyses of potential prognostic factors for PFS, 4 patients were excluded owing to positive TgAb, and a total of 68 patients were involved. In multivariate analyses of potential prognostic factors for OS, patients with positive TgAb (n = 4) or salvage treatment (n = 12) were excluded, and a total of 56 patients remained. Pathologically well DTC, the absence of bone metastases, and biochemically nonineffective response were revealed as independent prognostic factors for superior PFS (p = .0115, .0001, and .0330, respectively). Moreover, ECOG PS ≤2, the absence of bone metastases, and biochemically nonineffective response were independent factors associated with better OS (p = .0017, .0022, and .0005, respectively). Other factors, including gender, age, lung-only metastasis, and HFS, were not independent prognostic factors for either PFS or OS (all p > .05; Table 3).

Discussion

TKI therapy is evolving at present, raising an issue of which candidates may more feasibly benefit from these agents. The present prospective, single-center, real-world study, using a relatively large sample size, primarily revealed the role of clinicopathological features in predicting response, PFS, and OS in patients with progressive RR-DTC treated with sorafenib, which could be of great value for further optimizing indications of the drug and improving clinical practice. A recent multicenter study from Korea aimed to define the role of a few clinicopathological characteristics of patients with RR-DTC treated with sorafenib. However, the clinical characteristics of the study subjects were similar to those of a phase III trial, which might not fully reflect a real-life clinical setting [10]. Compared with ideally randomized controlled clinical trials and clinical trial–derived research, the current study is more representative of the real-world setting, because patients with a broader scope of ECOG PS (0–4) and those without target lesion were enrolled in our clinical practice [7, 9].

The overall DCR of 77.3%, ORR of 21.7%, and median PFS of 17.6 months were in line with prior studies, including ours [15, 22]. The overall median OS of 28.9 months, however, was relatively shorter than that of 34.5 months reported by Schneider et al. in a phase II clinical trial [9]. This might be partially explained by the incorporation of indispensable patients with poorer performance status, which has been demonstrated by a median OS of only 6.67 months in ECOG PS >2 group in our study probably owing to relatively larger tumor burden and poorer side-effect tolerance. Besides, one recent study also has found that poor ECOG PS was associated with inferior PFS and OS for patients with RR-DTC treated with lenvatinib [23]. Although there is a consensus that TKI therapy should be initiated in patients with

progressive disease, especially in those with considerable tumor load or symptomatic disease, uncertainty exists on the optimal timing to start. Our findings hint that earlier intervention may be preferred rather than waiting until poor ECOG PS is achieved, which is expected to be verified by a dedicated clinical trial [24].

The regimen of 400 mg sorafenib twice daily was adopted by four phase I clinical trials; however, no patients with thyroid cancer were enrolled [25]. It was noteworthy that a high incidence of AEs and drug interruption had been observed in two phase II studies subsequently [11, 12]. Later, Waguespack et al. described a dramatic improvement in an adolescent with progressive RR-DTC who was treated with sorafenib using 200 mg twice daily [26], which has been previously demonstrated as a feasible approach with comparable efficacy by our team [15, 19, 20]. In the present study, lower incidences and less severity of AEs were certified by comparing with high-dose strategy (400 mg twice daily) with grade 3–4 HFS (1.4% vs. 7%–44%), diarrhea (2.8% vs. 6%–15%), weight loss (0% vs. 10%), fatigue (0% vs. 9%–16%), and hypertension (6.9% vs. 6%–16%) [9, 11, 12, 16]. Approximately 5.6% of our patients underwent dose interruption or withdrawal as a result of severe AEs, which was relatively lower than 18.7%–93.1% of the patients in trials with high-dose strategy [7, 11, 12, 27]. Even though severe AEs were controllable with proper medical interventions and were rarely life threatening, patients with interruption or withdrawal of TKIs might have a smaller magnitude of benefit versus those with continuous administration [28]. Comparable efficacy, favorable tolerability, and potentially relieved financial burden encouraged us to maintain this low-dose strategy, forecasting a well-designed comparison study comprehensively evaluating the priority of the above dosages.

Bone metastases predicted worse DCR (55.6% vs. 81.0%, $p = .041$), PFS (6.67 vs. 28.57 months, $p < .0001$), and OS (10.27 months vs. not reached, $p < .0001$) after sorafenib treatment. These findings were in accordance with the findings of Hoftijzer et al., who found a shorter PFS (47 vs. 69 weeks, $p = .0046$) [13], and of Schneider et al., who found an unfavorable OS (23 months vs. not reached, respectively, p value not shown) in patients with bone metastases [9]. Furthermore, bone metastasis was identified as an independent poor prognostic factor by multivariate analysis. Because several studies using varying dosages of sorafenib (800 mg twice a day, 400 mg twice a day, and 200 mg twice a day) pointed to bone metastasis as an unfavorable prognostic indicator [7, 13], we presume that bone metastasis may be refractory to sorafenib therapy, possibly owing to the lower VEGFR signal transduction in tumor compared with pure soft tissue involvement [29, 30]. Thus, in these cases, other therapeutic modalities including local treatment are still needed, particularly in those with life-threatening bone lesions.

Serum Tg, a key tumor marker for monitoring DTC after thyroidectomy and ^{131}I ablation, decreased precipitously in most of the patients after beginning sorafenib treatment, resulting in a biochemically effective response of 77.9%. However, the best decrease of ≥25% in serum Tg level was not significantly associated with better PFS or OS. The implications of Tg changes during TKI administration remain unclear, which may be partially explained by the diverse levels of tumor dedifferentiation among individuals [7, 31]. Notably, biochemically ineffective responses predicted extremely dismal prognoses; hence, monitoring serum Tg change is necessary for the clinical setting, particularly when it increases over 25% during the first 3 months of sorafenib administration.

Poorly DTC is rare, with an incidence that varies from less than 3% in Japan and the U.S. to 15% in Northern Italy [32, 33]. The aggressive nature of this tumor at the advanced stage makes management very difficult. Because disappointing DCR (33.3%) and median PFS (3.63 months) and OS (13.10 months) were demonstrated, and independent prognostic value on poorer PFS was confirmed, novel, more effective and safe therapies are urgently needed to be identified and tested for this entity.

Patients with lung-only metastasis exhibited more favorable ORR and PFS compared with other patients (35.7% vs. 11.1%, $p = .035$; 39.9 vs. 8.37 months, $p = .0016$, respectively), which is in line with previous results obtained by our team and others [14, 15]. Moreover, the benefit of sorafenib treatment for median OS in such patients was initially reported in the present study (not reached vs. 21.23 months, $p = .0005$); therefore, it seems that patients with progressive lung-only metastatic RR-DTC may be a more suitable indication of sorafenib therapy.

With respect to the molecular pathogenesis and nature of the disease, a simple categorization method base on the differentiation status was applied in the analyses of outcomes, avoiding possible overlap of criteria when RR-DTC was defined in more detail [4, 34]. Although no significantly statistical differences in DCR, PFS, or OS were identified between the ^{131}I-avid group and the non-^{131}I-avid group, superior ORR was achieved in the ^{131}I-avid group. Nevertheless, inconsistency between ORR and survival and subtly inferior median PFS and OS were unexpectedly observed in the ^{131}I-avid group, which may be partially explained by the higher ratios of patients with skeletal metastases (38.2% vs. 26.3% in PFS analyses and 40% vs. 26.7% in OS analyses, respectively), possibly higher tumor burden due to more courses of prior TSH stimulation before ^{131}I administration, and more attacks of probably overused ^{131}I [35–37]. Therefore, early identification of patients with RR-DTC with ^{131}I-avid foci, timely halt of redundant ^{131}I therapy, and incorporating other therapeutic modalities may be of great value [35, 38].

HFS occurred in as low as 43.1% of patients in the current study, which might be due to low dose regimen, regular use of urea cream, wearing comfortable shoes, avoiding hot water, and keeping hands and feet well hydrated [39]. In the present study, we first discovered that the occurrence of HFS was an independent factor for better DCR and ORR and was associated with better PFS and OS; this phenomenon has also been partially recognized in patients with hepatic carcinoma, in whom a better OS was associated with HFS occurrence [40]. Besides, this relationship may be attributed to the more intense antiangiogenesis effect of sorafenib in tumors than that in normal organs, such as the hand and foot [40, 41].

Median OS was significantly longer in the disease control group than in the PD group (not reached vs. 6.47 months, $p = .0001$). This indicates that once the disease is controlled, benefits to overall survival can be reasonably anticipated.

However, resistance to TKI is a common problem when treating RR-DTC, and there is a limited understanding of the mechanisms involved. Dadu et al. pointed out that other targeted agents are effective salvage treatments after sorafenib therapy failure, despite similar mechanisms of action, and should be offered to appropriate patients [42]. In the current study, 12 patients, who received salvage treatment after disease progression, had a significantly longer OS than others (not reached vs. 28.93 months, $p = .0410$). Because many studies have shown that thyroid cancer cells produce cytokines and chemokines [43], and some cases have reported the use of immune checkpoint inhibitors in anaplastic thyroid cancer, immunotherapies as salvage treatment may be of potential use in further studies [44, 45].

This study had a few limitations. First, some clinicopathological features were not included at the very beginning of the research, such as genetic status and fluorodeoxyglucose PET/CT information. Second, even though it was a single-center study with a relatively large sample size, the number of patients with certain clinicopathological features, such as locally advanced disease, poorly DTC, or ineffective biochemical response, was too small because of an inherently low constituent ratio, which may have compromised the statistic efficacy. Finally, the median OS was not yet reached in patients with lung-only metastasis, in those with no bone metastasis, and in the disease control group, indicating that an even longer follow-up is needed.

Conclusion

Our prospective, single-center, real-world data demonstrated that well differentiation, lung-only metastasis, absence of bone metastasis, and HFS are associated with more favorable radiological response, PFS, and OS, and response per se may even forecast OS. ECOG PS ≤2 and biochemically noninneffective response associate with superior PFS and OS. Salvage treatment may lengthen OS in patients with sorafenib therapy resistance. HFS is an independent predictor for better DCR and ORR, and ^{131}I-avidity for higher ORR. Well differentiation and ECOG PS ≤2 independently predict more favorable PFS and OS, respectively, whereas no bone metastasis and biochemically noninneffective response are independent prognostic factors for superior PFS and OS. The current research probably warrants the optimization of TKI therapy of RR-DTC.

Acknowledgments

We thank the patients and their family members for their participation in this study. We thank Bei Wang and Shujing Sun for data collecting. This study was sponsored by the National Natural Science Foundation of China (Grant 81671711) and Shanghai Key Discipline of Medical Imaging (Grant 2017ZZ02005).

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Disclosures

The authors indicated no financial relationships.

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