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Prognostic Significance of Neutrophil-to-Lymphocyte Ratio in Differentiated Thyroid Carcinoma Having Distant Metastasis: A Comparison With Thyroglobulin-doubling Rate and Tumor Volume-doubling Rate

YASUHIRO ITO, NAOYOSHI ONODA, MINORU KIHARA, AKIHIRO MIYA and AKIRA MIYAUCHI

Department of Surgery, Kuma Hospital, Kobe, Japan

Abstract. *Background/Aim: To date, thyroglobulin-doubling rate (Tg-DR) and tumor volume-doubling rate (TV-DR) of metastatic lesions have been identified as dynamic prognostic factors for differentiated thyroid carcinoma (DTC). In this study, we investigated the prognostic impact for another dynamic factor, the neutrophil-to-lymphocyte ratio (NLR), for DTC with distant metastasis. Patients and Methods: We enrolled 321 patients in total, and NLR at the first detection of distant metastasis (initial NLR) was collected for 312. Results: Patients with initial NLR >3 had a significantly poorer cause-specific survival than those with initial NLR ≤3. On multivariate analysis, initial NLR >3 was recognized as an independent prognostic factor together with Tg-DR >1/year, TV-DR >1/year, radioactive iodine-refractory distant metastasis, and distant metastasis to organs other than the lung. Conclusion: Careful observation and active therapies, including multitarget kinase inhibitors, are recommended for patients with NLR >3 at the first detection of distant metastasis or during follow-up.*

Differentiated thyroid carcinoma (DTC) arises from thyroid follicular cells and generally shows an indolent character. However, cases with some clinicopathological characteristics have a dire prognosis and distant metastasis is an important prognostic factor. Radioactive iodine (RAI) therapy after total thyroidectomy is a standard of care for DTC with distant metastasis, and recently, multitarget kinase inhibitors such as sorafenib (1) and lenvatinib (2) were adopted as a new line of therapy for RAI-refractory and progressive metastatic lesions.

There are two kinds of prognostic factors, static and dynamic factors, for patients with DTC. Static prognostic factors consist of the patient's age at surgery, tumor size, lymph node metastasis, distant metastasis, and extrathyroid extension, which are adopted in various staging systems, including the American Joint Committee on Cancer Staging System (3). Dynamic factors indicate factors showing time-dependent changes. In 1984, Miyauchi *et al*. demonstrated that the doubling time (DT) of plasma calcitonin significantly reflected the prognosis of patients with medullary thyroid carcinoma (4). In 2011, they showed that a short thyroglobulin (Tg) DT is a significant prognostic factor for distant metastasis-free survival and cause-specific survival (CSS) of Tg-antibody-negative patients with papillary thyroid carcinoma who underwent total thyroidectomy and were followed-up under thyrotropin suppression (5). In 2017, Sabra *et al*. investigated the prognosis of DTC with distant metastasis and showed that the tumor volume (TV) DT was useful for predicting the CSS of patients (6). Although DT is well validated for analyzing and expressing changes in tumor volume or serum tumor marker levels over time, it has two major limitations. Firstly, if the tumor volume or serum tumor marker level decreases over time, DT has a negative value. This creates a problem of discontinuity from DTs with positive values. Secondly, the magnitude of a DT is opposite to the magnitude of the tumor growth rate. If we take the inverse of DT (*i.e*. 1/DT), these limitations are resolved. Miyauchi *et al*. proposed calling this index the doubling rate (DR) because it indicates the number of doublings that occur per unit time (7). Negative values indicate a number that is halving. Using this concept, they analyzed the change in volume of papillary thyroid microcarcinomas (7). Similarly,

Correspondence to: Dr. Yasuhiro Ito, Department of Surgery, Kuma Hospital, 8-2-35 Shimoyamate-dori, Chuo-ku, Kobe, Hyogo 650-0011, Japan. Tel: +81 783713721, Fax: +81 783713723, e-mail: ito01@kuma-h.or.jp

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Tg-DR, the inverse of Tg-DT, is useful for continuously evaluating the change in Tg level.

Recently, another dynamic prognostic factor, the neutrophil-to-lymphocyte ratio (NLR) has been focused on. Previous studies showed that systemic inflammation is related to carcinoma progression (8-10), and NLR is an inflammatory marker, reflecting the imbalance between immune surveillance and tumor progression. A high NLR indicates an increased number of neutrophils by carcinoma progression and reduced number of lymphocytes by suppression of immunological surveillance, which might affect carcinoma development and the patient's prognosis. Indeed, previous studies showed that a high NLR reflects a poor prognosis for patients with carcinomas of various organs (11-20). To date, several studies have been published about the relationship in DTC between NLR and clinicopathological characteristics, including patient prognosis but our knowledge about these issues still remains fragmentary (21-29). In this study, we therefore investigated whether and how NLR reflects the prognosis of patients with distant metastasis of DTC in order to investigate its usefulness as a prognostic factor.

Patients and Methods

Patients. We enrolled 321 patients with DTC with distant metastasis detected by imaging studies such as RAI scintigraphy, computed tomography (CT), magnetic resonance imaging, and positron-emission tomography-CT scan between March 2005 and July 2019. In 100 patients, distant metastases were detected before initial surgery, and metastatic lesions of the remaining 221 were detected during postoperative follow-up. The cohort consisted of 79 males and 242 females, with a median age at the time of distant metastasis detection of 68 (range=9-88) years. Histology consisted of 253 papillary, 60 follicular and eight poorly differentiated carcinomas. All patients underwent total thyroidectomy in initial surgery or in stepped surgery. Organs with metastasis consisted of lung or pleura in 290 patients, bone in 65 patients, brain in six patients, liver in two patients, kidney in two patients, and axillar lymph node in one patient. Forty-one patients had distant metastasis in two or more organs. Local recurrence such as recurrence to the regional lymph node, thyroid bed, or soft tissue was also detected in 101 patients.

Follow-up after the detection of distant metastasis. After the detection of metastasis, 293 patients were administered RAI (3-1,026 mCi in total, median of 113 mCi) for the purpose of therapy, ablation or scintigraphy. The remaining 28 were not administered RAI because of poor performance status, poor general condition, or patient refusal. Other therapies for distant metastasis were external radiotherapy in 10 patients, surgery in seven, denosmab in 11, zoledronic acid in two, and multitarget-kinase inhibitors for 19 patients. All patients underwent thyroid-stimulating hormone suppression. Patients were asked to visit our clinic 2-4 times a year normally. For patients who were referred to other hospitals, we sent a questionnaire to ask their health condition once a year. The median follow-up period at our hospital was 53 (range=1-179) months and the median follow-up period overall was 62 (range=3-185) months. Follow-up period after the appearance of NLR >3 ranged from 1 to 132 months (median=32 months). To date, 72 patients have died of thyroid carcinoma.

Data collection. The NLR was calculated as the ratio between the neutrophil and lymphocyte commits. However, we did not calculate it when patients had inflammation of some kind (such as high white blood cell count and positivity for C-reactive protein). Moreover, data after RAI therapy and after external radiotherapy were not adopted because temporal NLR elevation at these time points was reported previously (35, 36). We set a cutoff of NLR at 3 because previous studies showed that in patients with DTC with distant metastasis, NLR >3 before treatment with lenvatinib significantly affected their CSS (32, 37). We collected NLR at the time of first detection of distant metastasis (initial NLR) in 312 out of 321 patients in our series. Of these 312 patients, the initial NLR was >3 in 39 (12.5%). Seventy-two patients had NLR>3 during postoperative follow-up. We adopted only the initial NLR for univariate and multivariate analyses (except for CSS for the whole cohort). We regarded patients with initial or follow-up NLR >3 which was repeated within one year as non-censored cases at the time of first achievement of NLR >3.

Tg-DT and TV-DT were calculated using the Doubling Time Progression Calculator (available from http://www.kuma-h.or.jp/english) as described previously (7, 38). For calculating TV-DT, we selected one metastatic lesion that developed most rapidly on CT scan. In each examination, the maximum diameter (D1) and the diameter in the direction perpendicular to the maximum diameter (D2) were measured. Tumor volume (V) was then calculated using the ellipsoid equation ($\pi/6 \times D1 \times D2 \times D2$). The formula is described below. Time (T) was the time interval between presentation and measurement.

$$a = \left(n \sum_{k=1}^{n} T_k \times \log(V_k) - \sum_{k=1}^{n} T_k \times \sum_{k=1}^{n} \log(V_k) \right) \Big/ \left(\sum_{k=1}^{n} T^2{}_k - \left(\sum_{k=1}^{n} T_k \right)^2 \right)$$

We then calculated the Tg-DR and TV-DR, the inverse of Tg-DT and TV-DT only when Tg value and tumor volume data were collected three times or more in sequential examinations. We did not calculate Tg-DR for Tg-antibody-positive cases nor TV-DR for cases with metastases that were impossible to accurately measure two dimensions for. In total, Tg-DR of 265 patients and TV-DR of 292 patients (274 lung or pleural and 18 bone metastases) were collected.

Statistical analysis. We used a chi-square test and Fisher's exact text for comparing variables. For time-sequence analysis, Kaplan–Meier method with log-rank test was used for univariate analysis and Cox hazard regression test for multivariate analysis. All statistical analyses were conducted using the StatView version 5.0 (SAS, Cary, NC, USA). A value of $p<0.05$ was considered significant.

Results

Relationship between high NLR and clinicopathological features. As described in the Patients and Methods section (Data collection), we enrolled 321 patients in total. NLR at

Table I. *Relationships between initial neutrophil-to-lymphocyte ratio >3 and clinicopathological features.*

Variable	Initial NLR, n (%)		Total	*p*-Value
	>3	≤3		
Age at the detection of distant metastasis				
≥55 Years	35 (14.5%)	206 (85.5%)	241 (100%)	0.0640
<55 Years	4 (5.6%)	67 (94.4%)	71 (100%)	
Distant metastasis				
RAI-refractory	27 (13.4%)	174 (86.6%)	201 (100%)	0.0979
RAI-avid	5 (7.1%)	79 (92.9%)	84 (100%)	
Unknown	-	-	27	
TV-DR				
>1/Year	12 (23.5%)	39 (76.5%)	51 (100%)	0.0101
≤1/Year	22 (9.4%)	211 (90.6%)	233 (100%)	
Not evaluable	-	-	28	
Tg-DR				
>1/Year	13 (26.0%)	37 (74.0%)	50 (100%)	0.0008
≤1/Year	16 (7.8%)	190 (92.2%)	206 (100%)	
Not evaluable	-	-	56	
Distant metastasis other than lung				
Yes	18 (25.7%)	70 (74.3%)	88 (100%)	0.0124
No	21 (9.8%)	202 (90.2%)	224 (100%)	

TV-DR: Tumor volume-doubling rate; Tg-DR: thyroglobulin-doubling rate.

the first detection of distant metastasis (initial NLR) was collected for 312 patients, and initial NLR was >3 in 39 of them (12.5%). Table I shows the relationships between clinicopathological features and initial NLR. Patients with TV-DR >1/year (p=0.0101), Tg-DR >1/year (p=0.0008), and the presence of distant metastasis to organs other than the lung (p=0.0124) had an initial NLR>3 at significantly higher incidence. Moreover, patients aged ≥55 years at the detection of distant metastasis (p=0.0640) and with RAI-refractory distant metastasis (p=0.0979) tended to have an initial NLR >3 more frequently than those under 55 years of age and with RAI-avid distant metastasis, respectively.

Relationship between various clinicopathological features and CSS. In the next step, we investigated the prognostic impact of various factors. Figure 1A shows Kaplan–Meier curves for CSS of patients according to initial NLR. Patients with an initial NLR >3 had a significantly poorer CSS (p<0.0001) than those with NLR ≤3, with 5-year CSS rates of 89.9% and 62.8%, respectively. The 10-year CSS rate of patients with initial NLR ≤3 was 74.3%, while that of patients with initial NLR >3 could not be calculated because the number of patients at risk became zero before 10-year follow-up. Seventy-two patients had a postoperative follow-up NLR>3, although not at the first detection of metastasis. Figure 1B shows the Kaplan–Meier curve for CSS of 111 patients (39 patients with initial NLR >3 and 72 patients with follow-up NLR >3) after their NLR reached >3. Five- and 10-year CSS rates of these 111 patients were 50.4% and 23.9%, respectively.

Prognostic significance of other factors is shown in Figure 2A-C; age ≥55 years at the detection of distant metastasis (p=0.0001), RAI-refractory distant metastasis (p=0.0046), and distant metastasis to organs other than the lung (p<0.0001) had significant prognostic impacts for CSS of patients. Patients with TV-DR >1/year of metastasis had significantly poorer CSS (p<0.0001) than those with TV-DR ≤1/year (Figure 2D). In Tg-antibody-negative patients, CSS of those with Tg-DR >1/year (p<0.0001) was significantly poorer than that of those with Tg-DR ≤1/year (Figure 2E).

Multivariate analysis for CSS of patients. We then performed a multivariate analysis for CSS of patients. As shown in Table II, an initial NLR >3 independently affected CSS of patients (p=0.0109), together with TV-DR >1/year (p=0.0006), Tg-DR >1/year (p<0.0001), RAI-refractory distant metastasis (p=0.0460), and metastasis to organs other than the lung (p=0.0010). Age ≥55 years at the detection of distant metastasis had a marginal prognostic significance for poorer CSS (p=0.0653).

Discussion

To our knowledge, this is the first study on the prognostic value of NLR for DTC with distant metastasis by enrolling

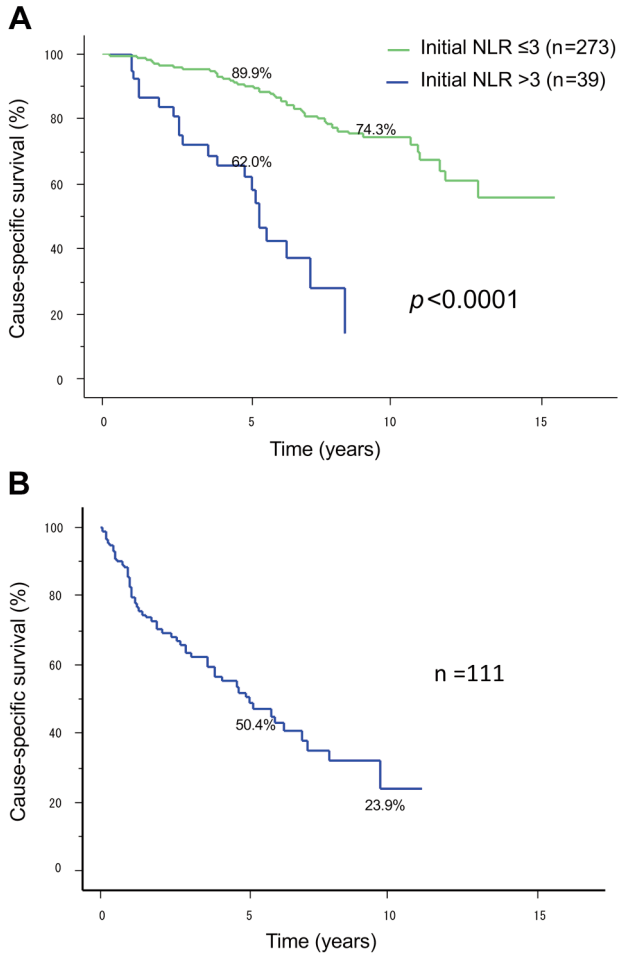

Figure 1. *A: Kaplan–Meier curves for cause-specific survival (CSS) of patients with differentiated thyroid carcinoma according to initial neutrophil-to-lymphocyte ratio (NLR). CSS of patients with initial NLR >3 was significantly poorer than that of those with initial NLR ≤3. B: Kaplan–Meier curve for CSS of patients with initial and follow-up NLR>3 after their NLR reaching >3.*

Table II. *Multivariate analysis of predictors for death from differentiated thyroid carcinoma.*

Variable	Hazard ratio (95% CI)	*p*-Value
Initial NLR >3	2.799 (1.267-6.184)	0.0109
TV-DR >1/year	3.388 (1.694-6.779)	0.0006
Tg-DR >1/year	4.233 (2.047-8.753)	<0.0001
RAI-refractory distant metastasis	2.791 (1.018-7.650)	0.0460
Age ≥55 years at detection of distant metastasis	3.237 (0.928-11.291)	0.0653
Distant metastasis other than the lung	3.452 (1.649-7.228)	0.0010

CI: Confidence interval; CI: confidence intervaI; HR: hazard ratio; NLR: neutrophil-to-lymphocyte ratio; TV-DR: tumor volume doubling rate; Tg-DR: thyroglobulin-doubling rate.

such a large number of patients (n=321). We demonstrated that in DTC with distant metastasis, an initial NLR >3 is a significant prognostic factor for CSS, together with patient age at the detection of distant metastasis (≥55 years), RAI-refractory distant metastasis, metastasis to organs other than the lung, Tg-DR >1/year and TV-DR >1/year. Furthermore, on multivariate analysis, an initial NLR >3 was recognized as an independent prognostic indicator for CSS of patients together with Tg-DR >1/year, TV-DR >1/year, the presence of RAI-refractory distant metastasis, and distant metastasis to organs other than the lung. These findings suggest that initial NLR has a strong prognostic value for CSS of DTC with distant metastasis. We analyzed the prognosis of patients with initial and follow-up NLR >3 and found that the CSS of these 111 patients was poor, the 10-year CSS rate being 23.9%, indicating that the elevation of NLR, not only at the first detection of distant metastasis, but also during follow-up, is also a sign of poor prognosis.

In the past, a few groups studied the prognostic value of NLR for the subset of patients with DTC. Lang *et al.* demonstrated that in a series of cN0 papillary thyroid carcinoma, high NLR was related to older age at operation and large tumor size, and low NLR was associated with low stage and distant metastasis, patient age, completeness of resection, local invasion, and tumor size score (27). However, in their series, high NLR was not a predictor of carcinoma recurrence or of occult central node metastasis. Kim *et al.* demonstrated that a high NLR (≥1.5) significantly affected disease-free survival of patients with stage III and IV papillary thyroid carcinoma only in univariate analysis (28). A meta-analysis showed that NLR of patients with DTC did not significantly differ from that of patients with benign nodules, indicating that an elevated NLR seems not to be a reliable indicator of progressive DTC in patients with goiters (29). They also showed that no difference in NLR was seen between patients aged <45 years and those aged ≥45 years, although age is a known strong prognostic factor. These findings indicate that a high NLR has a prognostic impact for DTC only to a limited extent.

More recently, Lee *et al.* investigated the relationship between change in post-treatment NLR compared with preoperative NLR and response to therapy in patients with DTC (30, 31). They showed that compared with the preoperative NLR, post-treatment NLR significantly decreased in patients classified as "excellent" and significantly increased in patients classified as "structural incomplete". They also showed that an increased NLR to be an independent predictor of an incomplete response to therapy. Fukuda *et al.* analyzed patients with DTC with

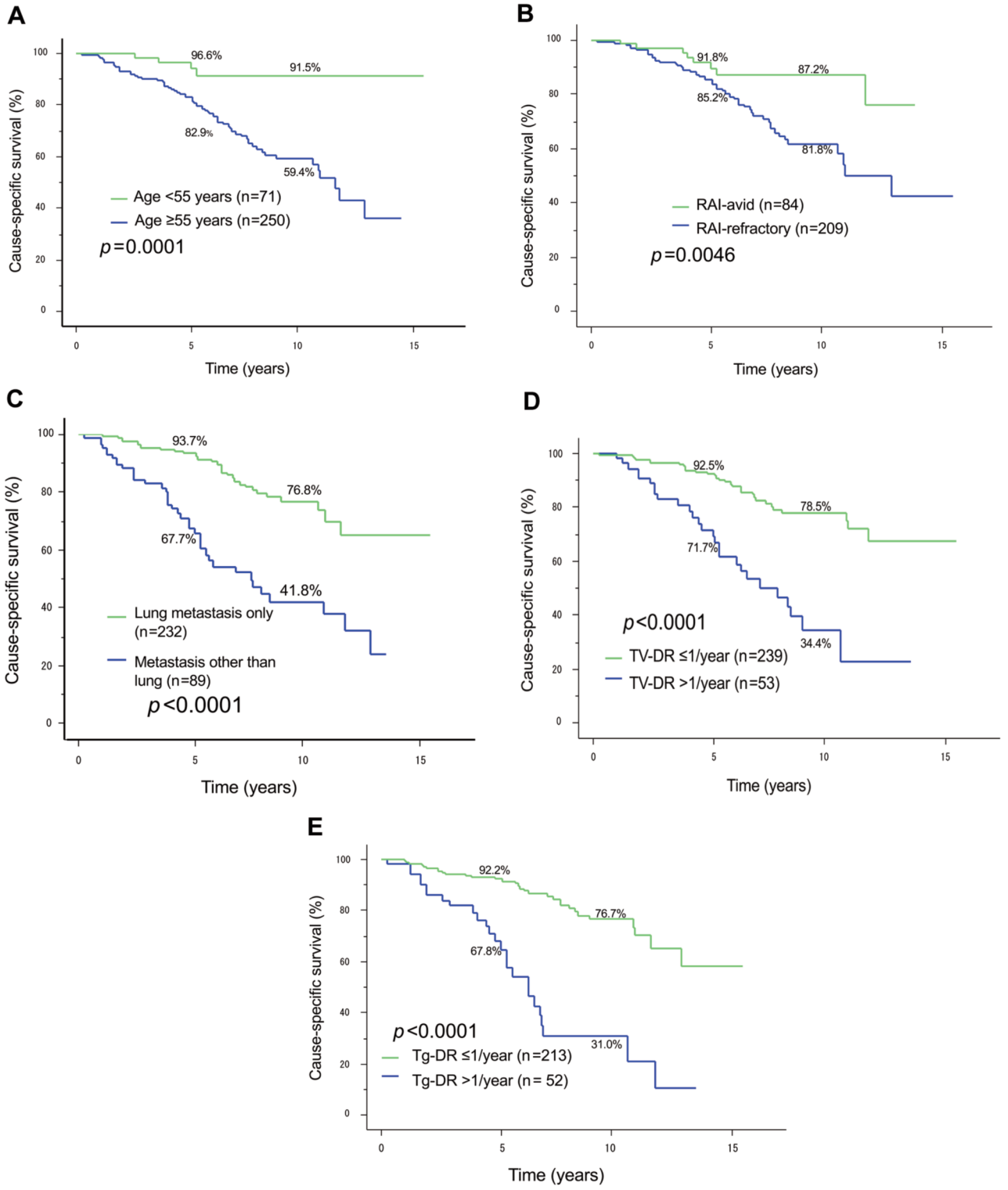

Figure 2. *Kaplan–Meier curves for cause-specific survival (CSS) of patients with differentiated thyroid carcinoma based on various clinical factors. A: CSS of patients aged ≥55 years was significantly poorer than that of those under 55 years of age. B: Patients with radioactive iodine (RAI)-refractory metastasis was significantly poorer than that of those with RAI-avid metastasis. C: CSS of patients with metastasis to organs other than the lung was significantly poorer that of those with metastasis only to the lung. D: CSS of patients with tumor volume-doubling rate (TV-DR) >1/year was significantly poorer than that of those with TV-DR ≤1/year. E: CSS of patients with thyroglobulin-doubling rate (Tg-DR) >1/year was significantly poorer than that of those with Tg-DR ≤1/year.*

RAI-refractory and progressive metastasis who were treated with lenvatinib (32). They reported that the median overall survival was significantly longer in patients with a low NLR (<3) at the start of lenvatinib therapy. They therefore concluded that NLR reflects disease activity and is usable as an indicator for starting lenvatinib treatment. These findings suggest the possibility that NLR is useful for evaluating disease progression and prognosis of patients with advanced DTC, including those with distant metastasis. Our findings in the present study that high NLR has a strong prognostic value of DTC with distant metastasis are consistent with these recent findings. Previous studies showed high NLR in anaplastic thyroid carcinoma [33, 34], which also indicates that a high NLR significantly reflects aggressive behavior of thyroid carcinoma derived from follicular cells.

Our study has some limitations. This was a retrospective study and some sequential data of patients were lacking. Although we made an effort to collect patient outcomes by sending questionnaires as much as we were able to, some patients were still lost to follow-up. Despite this, our study clearly showed the prognostic impact of a high NLR for patients with DTC with distant metastasis.

In conclusion, in patients with distant metastasis of DTC, like the Tg-DR and TV-DR, an NLR >3 is an independent dynamic prognostic factor. Therefore, for patients with an NLR >3 at the first detection of distant metastasis or during the post-treatment follow-up, careful observation and active therapies, including a systemic therapy using multi-target inhibitors, are recommended.

Conflicts of Interest

Authors declare no conflicts of interest associated with this article.

Authors' Contributions

Y.I. and N.O. had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Conceptualization: Y.I., N.O., and A.M. (Akira Miyauchi). Investigation: Y.I., and N.O. Formal analysis: Y.I. Writing-original draft: Y.I., and N.O. Supervision: M.K., A.M. (Akihiro Miya), A.M (Akira Miyauchi). All Authors have read and agreed to the published version of the article.

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