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Methionyl-tRNA synthetase 1 expression, the possibility as a diagnostic and prognostic factor in papillary thyroid cancer

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Abstract

Background Methionyl-tRNA synthetase 1 (MARS1) is a critical enzyme in translation initiation, responsible for catalyzing the transfer of Met to the initiator tRNA. In this study, we aimed to examine whether MARS1 expression is different between normal follicular cells and papillary thyroid carcinoma (PTC) cells in thyroid tissue and whether it can supplement the limitations of general cell staining methods currently performed for diagnosis of PTC.

Methods Initially, 103 patients were included to compare MARS1 expression in PTC and normal follicular cells. Next, 100 patients were selected to compare MARS1 expression using immunohistochemical analysis in patients with ($n=50$) and without ($n=50$) lateral neck metastasis.

Results The average MARS1 expression grade of PTC cells was 2.59 and that of normal follicular cells was 1.28. MARS1 expression in the two groups showed significant differences ($p<0.001$). There was a significant difference in the average MARS1 expression grade of PTC cells between the metastasis and non-metastasis groups ($p<0.05$). Additionally, a significant difference was observed in the average MARS1 expression grade between the lymph node of the metastasis group and PTC cells of the non-metastasis group ($p<0.05$).

Conclusions Our analyses suggest that MARS1 could be used as a complementary method to the current fine needle aspiration biopsy tissue staining method. Additionally, MARS1 could be a predictor of the prognosis of PTC.

Keywords Papillary thyroid cancer, Methionyl-tRNA synthetase 1, Diagnostic marker, Prognostic marker

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Background

Thyroid nodules are generally found on ultrasound scans performed for cervical screening [1]. Further determination of whether there is a need for observation or additional tests depends on the size and shape of the nodules and whether they classify as hot or cold nodules. Fine needle aspiration biopsy (FNAB) is an important and widely accepted method used in the diagnosis of patients with thyroid nodules [2].

The results of FNAB are largely divided into 6 categories, according to the Bethesda system for reporting thyroid cytopathology (TBSRTC), of which surgical treatment is generally performed in categories 5 or 6 [3]. However, in categories 3 and 4, the Bethesda system is ambiguous about whether surgery is required. Category 3 refers to an atypical cell, and generally, surgical treatment is considered when successive FNAB results depict category 3 [4]. Category 4 refers to follicular neoplasm, and in this case, it is not possible to confirm a possibility of malignancy with FNAB [5]. The malignancy in category 4 can only be confirmed at the final pathology after surgery. In categories 3 and 4 of TBSRTC, excessive tests or surgical treatments may be performed. This can be considered a limitation of the general FNAB tissue staining method currently being performed [6].

Methionyl-tRNA synthetase 1 (MARS1) plays an essential role in initiating translation by transferring Met to initiator tRNA and has a close relationship with aminoacyl-tRNA synthetase-interacting multifunctional protein-3 (AIMP3)/p18, a potent tumor suppressor that is translocated to the nucleus for DNA repair upon DNA damage [7]. MARS1 an aminoacyl-tRNA synthetase (ARS), which is responsible for synthesizing synthesizing cellular proteins [8]. Recently, a number of studies have indicated that ARSs are also involved in a variety of physiological and pathological processes, especially tumorigenesis. ARSs can be used as diagnostic and prognostic biomarkers for cancer patients. Several studies have reported malignancy based on elevated MARS1 expression detected by immunostaining [9].

In this study, we aimed to examine whether MARS1 expression differs between normal follicular cells and papillary thyroid cancer (PTC) cells in the thyroid tissue and verify whether it can supplement the limitations of the currently used general cell staining methods.

Methods

Study design

In this retrospective study, tissues were obtained from patients who underwent surgical treatment for PTC. First, we selected 103 patients diagnosed with PTC from May 8, 2020 to June 8, 2022 to compare MARS1 expression between PTC cells and normal follicular cells obtained from the thyroid tissue of the patients. Second, we selected 100 patients who underwent bilateral thyroidectomy with or without modified radical neck dissection between July 09, 2015 and December 14, 2017, and compared the MARS1 expression in patients with lateral neck metastasis and those without. The reason for selecting an earlier patient cohort than the first group was to include a 5-year follow-up for recurrence in the outcome analysis. Of the 100 patients, 50 had lateral neck metastasis and the remaining 50 had no metastasis. For patients with lateral neck metastasis, modified radical neck dissection was performed and lateral neck lymph node was confirmed by permanent pathology. This study was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital, Yonsei University College of Medicine (IRB protocol: 3–2020-0309). Given the retrospective nature of the study, the requirement for patient approval or informed consent was waived by the IRB.

Immunohistochemical staining

Immunohistochemical (IHC) staining for MARS1 was performed on paraffin-embedded thyroid tissue blocks cut into 4 μm sections using an automated IHC stainer (BenchMark XT; Ventana Medical Systems, Tucson, AZ, USA) with a primary antibody against human MARS1 (1:300; 0.2 mg/mL; Bicbio Inc., Suwon, South Korea).

Interpretation of MARS1 expression

MARS1 expression in PTC and normal follicular cells was categorized into four grades (Grade 0, 1, 2, 3) depending on the intensity of the expression. If the MARS1 expression staining intensity in the thyroid tissue was similar to that in the parathyroid gland or germinal center cells of lymphoid tissue, it was determined as Grade 3. If the MARS1 expression staining intensity in thyroid tissue was similar to that in benign thyroid follicles, it was determined as Grade (1) MARS1 expression staining intensity between Grades 1 and 3 was determined as Grade (2) If MARS1 was not expressed in the sample, it was determined as Grade 0. Figure 1 shows Grades 1, 2, and 3 MARS1 expression in thyroid tissues along with Grade 3 MARS1 expression in metastatic PTC cells in the lymph node.

Statistical analysis

All statistical analyses were performed using SPSS 27 statistical software. Fisher's exact or chi-square tests were used to compare categorical variables. Student's *t*-test was used to compare continuous variables, which are presented as mean ± standard deviation. Statistical significance was set at $p < 0.05$.

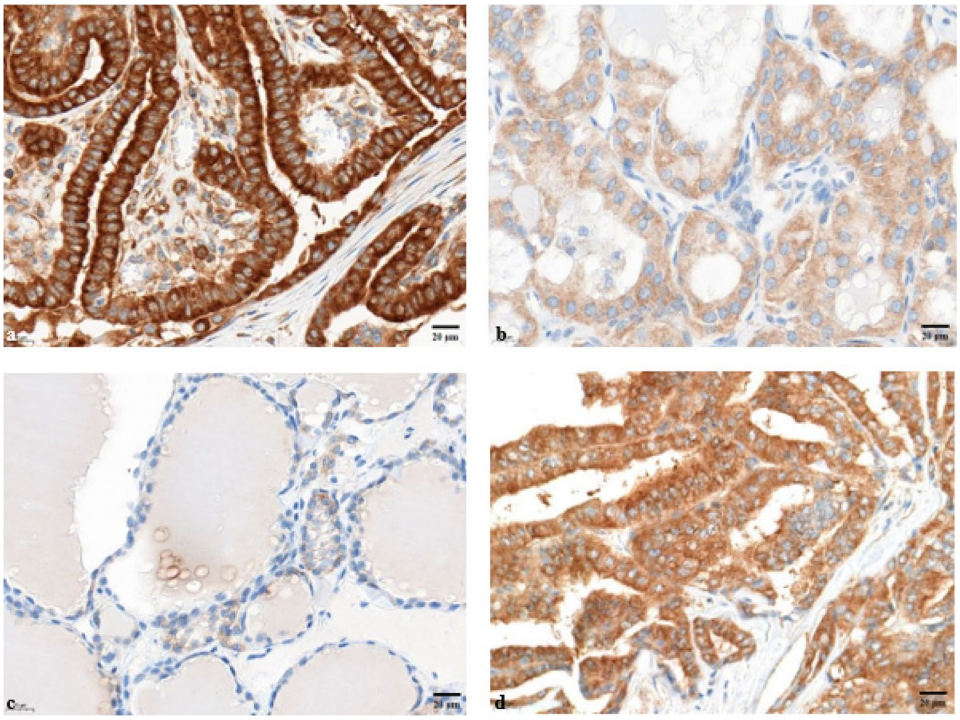


Fig. 1 MARS1 expression in thyroid tissue. Grade 3 (**a**) and Grade 2 (**b**) expression in papillary thyroid carcinoma cells, and grade 1 (**c**) expression in normal thyroid follicular cells (Magnification: 400×). Grade 3 expression in metastatic papillary thyroid carcinoma cells in lymph node (**d**) (Magnification: 400×)

Table 1 Clinical features of 85 patients enrolled for determination of MARS1 expression

Parameter	Values
Total number	85
Sex	
Male	22 (26%)
Female	63 (74%)
Surgical extent	
Total	34 (40%)
Less than total	51 (60%)
Lateral neck dissection	
No	74 (87%)
Unilateral	9 (11%)
Bilateral	2 (2%)
Thyroiditis	
Yes	29 (34%)
No	56 (66%)
Extra-thyroidal lesion	
Yes	9 (11%)
No	76 (89%)
Age (years)	44.53 ± 11.649
Size (cm)	1.05 ± 0.759
Positive Central LN	1.82 ± 2.980
Total Central LN	5.33 ± 4.164

The data are presented as n (%) or mean ± standard deviation

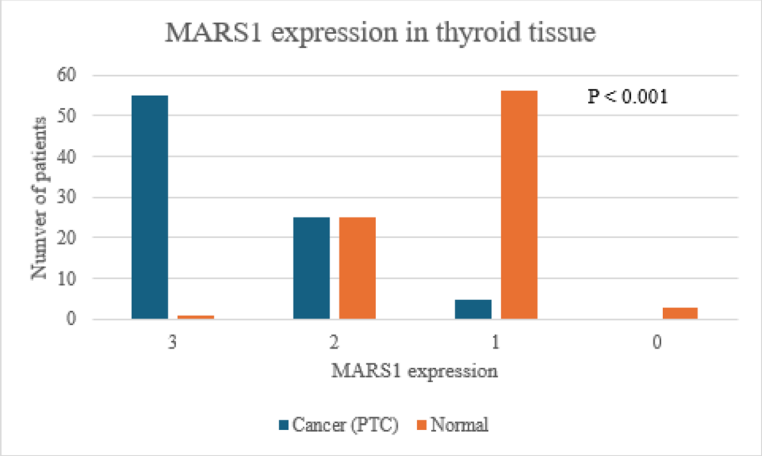
LN Lymph node

Results

MARS1 expression in normal follicular and PTC cells

We obtained both normal and cancer tissues from 103 patients, 18 of whom were excluded as IHC evaluation result was insufficient. All patients had a preoperative FNAB-confirmed diagnosis of cancer, classified as Bethesda Category 5 or 6. Table 1 shows the clinical features of the remaining 85 enrolled patients. The number of female patients was 63 (74.1%), and the average age was 44.52 years. The average tumor size was 1.05 cm. Total thyroidectomy was performed for 34 patients, and the remaining 51 patients underwent a partial thyroidectomy. Modified radical neck dissection (MRND) was conducted in 11 patients, two of whom underwent bilateral MRND. The average number of harvested central lymph nodes was 5.33, and the average number of metastatic central lymph nodes was 1.82.

Figure 2 shows the comparison of MARS1 expression between PTC cells and normal follicular cells in thyroid tissues. Fifty-five patients showed Grade 3 expression in PTC cells. Grade 2 expression was found in 25 patients, and Grade 1 expression in 5 patients. No patient with PTC cells was categorized under Grade 0 MARS1 expression. Fifty-six patients had Grade 1 expression in normal follicular cells. Grade 2 expression was found in 25 patients, and Grade 3 expression in only 1 patient. Three patients showed Grade 0 expression. The average MARS1 expression in PTC cells was 2.59 and that in normal



MARS1 expression	3	2	1	0	Total	Average
Cancer (PTC)	55	25	5	0	85	2.59 ± 0.603
Normal	1	25	56	3	85	1.28 ± 0.548

PTC, Papillary thyroid carcinoma; MARS1, Methionyl-tRNA synthetase 1

The data are presented as n (%) or mean ± standard deviation.

Fig. 2 MARS1 expression in cells of 85 patients with thyroid cancer. MARS1 average expression grades (0, 1, 2, or 3) in papillary thyroid carcinoma (PTC) cells and normal follicular cells of 85 patients with PTC

follicular cells was 1.28, with the two groups showing significant differences ($p < 0.001$).

MARS1 expression with and without lateral neck metastasis

We selected 100 patients to compare MARS1 expression between patients with ($n = 50$) and patients without ($n = 50$) lateral neck metastasis. All patients had a preoperative FNAB-confirmed diagnosis of cancer, classified as Bethesda Category 5 or 6. Thyroid cancer tissues were obtained from all patients, and lymph node tissues were obtained from patients with lateral neck metastasis. The clinical features of the enrolled patients are shown in Table 2. Each group comprised 10 male and 40 female patients, and total thyroidectomy was performed for all patients. In the metastasis group, two patients underwent bilateral MRND, while unilateral MRND was performed for the remaining. The average age of each group was 48.78 and 40.62 years, respectively ($p = 0.001$). The average tumor size was 1.45 cm for patients who underwent MRND and 1.34 cm for the rest ($p = 0.096$). The average number of harvested central lymph nodes was 7.20 and 8.18 ($p = 0.376$), while those of harvested metastatic central lymph nodes was 1.38 and 4.14 ($p = 0.000$), in patients who did not undergo MRND and those who did, respectively. There was a difference in the 5-year recurrence numbers (2 and 5 in each group); however, owing to the small sample size, this difference was not statistically significant ($p = 0.433$).

Figure 3 shows the comparison of MARS1 expression between the lateral neck metastasis group and no metastasis group. In the no metastasis group, 33 patients had Grade 3 expression. Grade 2 expression was found in 17 patients, and none of patients showed Grade 1 expression. In the group with lateral neck metastasis, 49 patients showed Grade 3 expression and only 1 patient showed Grade 2 expression. In the group of patients with lateral neck lymph node, 45 patients showed Grade 3 expression and 5 showed Grade 2 expression. In the group without metastasis, the average MARS1 expression grade was 2.66 ± 0.479, and in patients with metastasis, the average was 2.98 ± 0.141. The average number of positive lymph nodes in patients with lateral neck metastasis was 2.90 ± 0.303. There was a significant difference in the average MARS1 expression grade in PTC cells between the metastasis and non-metastasis groups ($p < 0.05$). There was also a significant difference in the average MARS1 expression grade between the lymph nodes of the metastasis group and PTC cells of the non-metastasis group ($p < 0.05$). There was no difference in

Table 2 Clinical features of patients divided into LND (-) and LND (+) groups based on whether they underwent lateral neck dissection

Parameter	LND (-)	LND (+)	*p*-value
Total number	50	50	
Sex			
Male	10 (20%)	10 (20%)	
Female	40 (80%)	40 (80%)	
Surgical extent			
Total	50	50	
Lateral neck dissection			
Unilateral	-	48 (96%)	
Bilateral	-	2 (4%)	
Thyroiditis			
Yes	20 (40%)	25 (50%)	
No	30 (60%)	25 (50%)	
Extra-thyroidal lesion			
Yes	-	21 (42%)	
No	50	29 (58%)	
Age	48.78 ± 12.508	40.62 ± 10.665	0.001
Size	1.34 ± 0.340	1.45 ± 0.313	0.096
Positive Central LN	1.38 ± 2.285	4.14 ± 4.131	0.000
Total Central LN	7.20 ± 5.632	8.18 ± 5.390	0.376
Positive Lateral LN	-	4.42 ± 3.535	-
Total Lateral LN	-	28.92 ± 14.023	-
Recurrence (5years f/u)	2 (4%)	5 (10%)	0.433

The data are presented as n (%) or mean ± standard deviation

LND Lateral neck dissection, *LN* Lymph node

the average MARS1 expression grade between the lymph nodes and PTC cells of the metastasis group ($p = 0.94$).

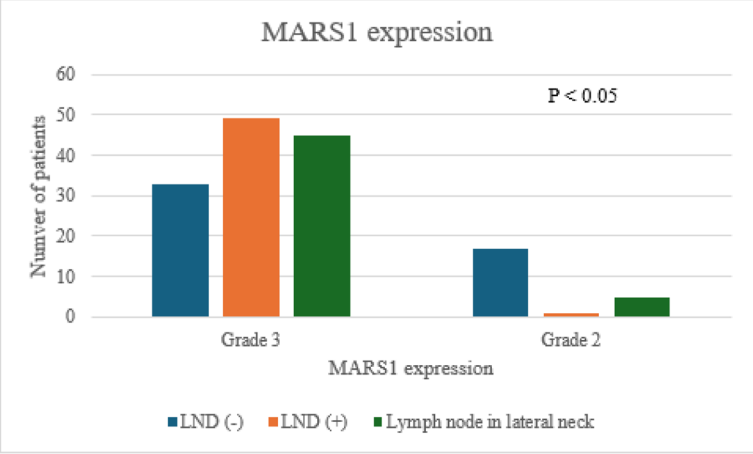
Discussion

Elevated MARS1 expression in carcinoma can be used to diagnose malignancy of indeterminate specimens in several cancers. In the biliary stricture, the high sensitivity and accuracy of MARS1 immunofluorescence staining enables the detection of malignancy in patients with biliary strictures [10]. Furthermore, high MARS1 expression in pancreatic ductal adenocarcinoma could be associated with a poor prognosis [11]. In non-small-cell lung cancer (NSCLC), MARS1 staining has shown good diagnostic performance for determining lymph node metastasis [12]. MARS1 is also associated with poor clinical prognosis in NSCLC [13]. In our study, we found that MARS1 could perform the same role in PTC.

The average MARS1 expression was higher in PTC cells than in normal thyroid follicular cells. This could compensate for the vulnerability of conventional FNAB that diagnoses thyroid nodules. When FNAB is carried out for the diagnosis of thyroid nodules, TBSRTC is used to describe the result of FNAB [3]. In this system, Category 3 (Atypia or undetermined) and Category 4 (Follicular neoplasm) are not considered "confirmed cancer" but have a possibility to be diagnosed as thyroid cancer at the permanent pathology. Therefore, when patients are diagnosed as Category 3 or 4 after FNAB, the surgery option cannot be excluded and, in practice, thyroidectomy is often performed [14]. If the final pathology does not determine cancer, the surgery performed becomes an unnecessary procedure that was done to rule out the possibility of cancer. Determining MARS1 expression grade has the potential to help avoid this unnecessary process. If the MARS1 expression grade with FNAB is high, surgery would be a reasonable option. If the MARS1 expression grade with FNAB is low or similar to that in normal tissues, the option of surgery could be held off in favor of follow-ups.

Another aim of this study was to examine the hypothesis that MARS1 is a possible marker for prognosis in thyroid cancer. Patients with lateral neck metastasis showed a higher average MARS1 expression grade than patients without lateral neck metastasis. Considering that thyroid cancer with lateral neck metastasis is aggressive, the higher MARS1 grade expression could be associated with more aggressive thyroid cancer. Although the precise mechanism underlying the high expression of MARS1 in PTC is not fully understood, several studies on ARSs suggest that dysregulated aminoacyl-tRNA synthetases may contribute to tumor progression by affecting DNA repair, cell cycle regulation, and metastatic potential [8, 9]. Given the known interaction between MARS1 and AIMP3/p18, a tumor suppressor involved in DNA repair, it is plausible that altered MARS1 expression may disturb this pathway, thereby promoting genomic instability and enhancing metastatic behavior [7]. This mechanistic link may explain the observed association between elevated MARS1 expression and lymph node metastasis in PTC. Further studies including comparison between groups and the patients' overall survival are needed to elucidate the relationship between MARS1 expression and prognosis of thyroid cancer.

There are several limitations to this study. First, this is a single center retrospective study, and the study population is small. Second, we did not evaluate the actual diagnostic effectiveness of MARS1 in TBSTRC Category 3 and Category 4. Additional studies on Category 3 and Category 4 with MARS1 expression grade would be needed to determine the effectiveness of MARS1 expression as a diagnostic factor. Third, there were potential sources of bias in the statistical analysis. For example, we could not exclude the possibility that MARS1 expression in the study population was influenced by other malignant tumors or severe underlying diseases in addition to thyroid cancer. Furthermore, in the comparison between MARS1 expression and lymph node metastasis, we did not adequately account for potential confounding factors such as age or other clinical variables beyond MARS1



MARS1 expression	3	2	1	Total	Average
LND (-)	33	17	0	50	2.66 ± 0.479
LND (+)	49	1	0	50	2.98 ± 0.141
Lymph node in lateral neck	45	5	0	50	2.90 ± 0.303

MARSI, Methionyl-tRNA synthetase 1; LND, Lateral neck dissection

The data are presented as n (%) or mean ± standard deviation.

Fig. 3 MARS1 expression in lateral neck dissection (LND) group and without LND group. Comparison of average MARS1 expression grades (0, 1, 2, or 3) between patients with and without lateral neck metastasis

itself. Future studies will aim to address and control for these factors.

In conclusion, we found that MARS1 expression could be used as a complementary method to the current FNAB tissue staining method for cancer diagnosis. Furthermore, the average MARS1 expression in PTC and normal follicular cells showed significant differences, reinforcing its potential as a diagnostic marker that can also predict prognosis in thyroid cancer cases.

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Authors' contributions
Conceptualization: S.M.K, J.H.N.; Data curation: J.S.L, S.K.P.; Formal analysis: J.S.L, S.K.P.; Investigation: J.S.L.; Methodology: S.M.K.; Project administration: S.M.K., J.H.N.; Resources: J.S.L.; Software: S.K.P.; Supervision: S.M.K.; Validation: J.S.L., S.M.K.; Visualization: J.S.L, S.K.P., J.H.N.; Writing – original draft: S.K.P, J.S.L.; Writing – review & editing: H.J.J, H.J.Y, S.M.K, J.H.N, H.J.C, Y.S.L, H.S.C.; Approval of final manuscript: all authors.

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Data availability
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital, Yonsei University College of Medicine (IRB protocol: 3-2020-0309). Given the retrospective nature of the study, the requirement for patient approval or informed consent was waived by the IRB.

Consent for publication
Not applicable in this manuscript.

Competing interests
The authors declare no competing interests.

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