Endocrine Journal 2025, 72 (5), 535-543. doi:10.1507/endocrj.EJ24-0557

ORIGINAL

Assessing the potential of high-mobility group AT-hook 2 immunohistochemical staining as a prognostic marker of metastatic recurrence in follicular thyroid cancer: a retrospective cohort study

Yuka Ito[1], Junko Sakumoto[1], Hideki Hirabayashi[2], Shinichi Haruna[2], Wataru Konno[2], Itsuo Nakajima[2], Kazuyuki Ishida[3], Yasuo Haruyama[4], Toshimi Sairenchi[5], Eijun Nishihara[6], Shuji Fukata[6], Akira Hishinuma[7] and Takahiko Kogai[1]

[1] *Department of Genetic Diagnosis and Laboratory Medicine, Dokkyo Medical University, Tochigi 321-0293, Japan*
[2] *Department of Otorhinolaryngology, Head and Neck Surgery, Dokkyo Medical University, Tochigi 321-0293, Japan*
[3] *Department of Diagnostic Pathology, Dokkyo Medical University, Tochigi 321-0293, Japan*
[4] *Department of Public Health, Dokkyo Medical University, Tochigi 321-0293, Japan*
[5] *Medical Science of Nursing, Dokkyo Medical University School of Nursing, Tochigi 321-0293, Japan*
[6] *Kuma Hospital, Hyogo 650-0011, Japan*
[7] *Hishinuma Clinic, Kanagawa 239-0841, Japan*

Abstract. High-mobility group AT-hook 2 (HMGA2) is a nuclear protein involved in the differentiation and proliferation of epithelial-derived tumors and also considered to be involved in the growth and differentiation of various malignant tumors, including thyroid cancer. Immunohistochemistry (IHC) for HMGA2 has been reported to show diffuse positivity in several follicular thyroid carcinoma (FTC) cases. This study aimed to investigate whether positive immunohistochemical staining for HMGA2 in primary tumors can be used to predict the prognosis and detect prognostic factors in malignant thyroid tumors associated with metastatic recurrence in FTC. Formalin-fixed, paraffin-embedded (FFPE) resected specimens used for the IHC for HMGA2. The association of positive HMGA2 staining with metastasis and recurrence, along with the potential of HMGA2 as a prognostic marker of metastatic recurrence, was statistically determined. HMGA2 staining was positive in most malignant tissues, whereas benign tissues were unstained. HMGA2 staining of the marginal and invasive regions was observed in FTC tissues. The association of HMGA2 staining with metastasis and recurrence was significant ($p = 0.018$). Kaplan-Meier curves showed an association of negative HMGA2 staining with metastasis and disease-free survival ($p = 0.090$). Tumor size (>4 cm) and wide invasion were also significant factors ($p = 0.043$, $p < 0.001$). The risk ratio without HMGA2 was significantly reduced by 30% compared to that with HMGA2. In primary tumors, positive HMGA2 staining can be used to predict prognosis in malignant thyroid tumors associated with metastatic recurrence in FTC and negative HMGA2 staining may indicate longer disease-free survival after surgery.

Key words: High-mobility group AT-hook 2 (HMGA2), Metastatic recurrence, Follicular thyroid carcinoma (FTC), Prognosis, Immunohistochemistry (IHC)

Introduction

High-mobility group AT-hook 2 (HMGA2) is a high-mobility group (HMG) protein. It is a non-histone chromatin-associated protein that binds to adenine-rich and thymine-rich (AT-rich) hooks of DNA that exist in the minor grooves [1]. HMGA2 protein is encoded by the *HMGA2* gene, which functions as an architectural factor to regulate transcription and maintain the structure of chromatin prog [1]. Several studies have reported that HMGA2 is overexpressed in various malignant tumors [2]. HMGA2 is essential for early embryogenesis and oncogenesis because it plays an essential role in epithelial-mesenchymal transition (EMT), a process that causes morphological changes from epithelial to mesenchymal cells [3]. Thus, cancer recession is accelerated by the activation of several HMGA2 pathways [1]. For example, EMT plays a significant role in tumor progression,

Submitted Oct. 9, 2024; Accepted Jan. 5, 2025 as EJ24-0557
Released online in J-STAGE as advance publication Feb. 19, 2025
Correspondence to: Yuka Ito, MD, Department of Genetic Diagnosis and Laboratory Medicine, Dokkyo Medical University, 880 Oojikitakobayashi, Mibu, Tochigi 321-0293, Japan.
E-mail: yuka-ito@dokkyomed.ac.jp

metastasis, and drug resistance in colorectal cancer [4]. Particularly, an association between HMGA2 expression and tumor metastasis has been reported. HMGA2 expression has a high potential for improving the diagnosis of follicular neoplasms of the thyroid [5]. Moreover, it has also been reported as an independent prognostic factor for both perihilar and distal cholangiocarcinoma [6].

Thyroid cancer is one of the most common endocrine tumors with the lowest mortality rate [7]. Differentiated cancers derived from the follicular thyroid cell lineage include papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). PTC accounts for 90% of all thyroid cancers, and FTC, the second most prevalent type, accounts for approximately 10% of all cases [7]. In contrast, undifferentiated cancers, including medullary thyroid cancer and ATC, account for less than 5% of all cases [7]. Compared with PTC, FTC is more difficult to diagnose and prognose. This can be attributed to the following reasons. First, FTC is diagnosed based on follicular structure, capsular invasion, and vascular invasion. However, these characteristics cannot be clearly discerned using conventional hematoxylin–eosin (HE) staining. For example, the cell morphology of FTC, benign tissues, and follicular adenoma (FA) can hardly be distinguished using HE staining. Second, most patients with PTC have good long-term survival, but the prognosis of patients with FTC is worse as it easily metastasizes to bones, lungs, and lymph nodes. Some studies have suggested that survival and mortality rates depend on the degree of capsular or vascular invasion, age, and presence or absence of distant metastasis [7]. FTC has a poorer prognosis than PTC, and their prognostic factors differ [8-14]. Some prognostic factors of FTC have been investigated, especially in Japan.

Ito *et al.* investigated whether and how well the 8th edition of the tumor-node-metastasis (TNM) staging system reflected the cause-specific survival (CSS) of patients with PTC by analyzing the cases in 5,892 patients who underwent initial surgery between 1987 and 2005. Using the 7th edition, the CSS of patients with stage IVA and stage III disease was similar. In contrast, using the 8th edition, CSS was poorer in stage II than in stage I, in stage III than in stage II, and in stage IVB than in stage III. Similar results were observed for disease-free survival (DFS) [15]. Several studies have indicated age (≥45 years), tumor size defined as the maximum diameter of the resected primary tumor (>4 cm), and wide invasion as prognostic factors of FTC [9, 11, 12, 16-22]. Patients with minimally invasive FTC and those aged ≥45 years have been reported to demonstrate poorer DFS than those aged <45 years [18].

Previous studies have shown that HMGA2 expression has a wide range of sensitivity and specificity for the differentiation of malignant thyroid tissues [23-26] and that HMGA2 is significantly overexpressed in thyroid carcinoma compared to benign tumors [27]. Chromosomal translocations previously associated with human tumors reportedly disrupt the repression of HMGA2 by let-7 miRNA [28].

In PTC, EMT is associated with aggressiveness regulated by vimentin [29]. Molecular studies have shown that HMGA2 may be useful in distinguishing between benign and malignant thyroid tumors [30]. Overexpression of miRNA98-5p reportedly inhibits cell growth by inducing apoptosis and suppressing HMGA2 protein expression in PTC through suppression of HMGA2 [31]. The signaling pathway from thyroid transcription factor 1 (TTF-1) to HMGA2, which is important for controlling lung cancer metastasis, is mediated by miR-33a [32]. HMGA2 plays an important anticancer role in PTC [33].

Immunohistochemistry (IHC) for HMGA2 has been reported to show diffuse positivity in many FTC cases. Thus, HMGA2 staining could be beneficial in differentiating FTC [34]. Therefore, this study aimed to investigate whether positive immunohistochemical staining for HMGA2 in primary tumors can be used to predict the prognosis in malignant thyroid tumors associated with metastatic recurrence in FTC [35].

Materials and Methods

Study participants

We examined 26 thyroid samples retrieved from surgical pathology files of Kuma Hospital (Kobe, Japan). These included five cases of PTC, three cases of FTC, three cases of anaplastic cancer (ATC), three cases of adenomatous goiters (AG), one case of FA, and 11 normal thyroid tissues after thyroidectomy diagnosed according to WHO classification [7]. In this retrospective cohort study, 44 thyroid samples were collected from patients with FTC whose electronic records were available after thyroidectomy at Dokkyo Medical University Hospital, including patients who were already diagnosed with M1 at the time of surgery. The mean follow-up duration was 9.94 years (median 9.0 years; range 0–36 years between 1986–2022). The age of the patients ranged between 18–86 years (median, 53.5 years). The average thyroid nodule size was 3.82 cm (median, 3.5 cm; range, 0.8–9.5 cm).

Evaluation for immunohistochemical examination

IHC staining of HMGA2 was performed using 4-μm-thick sections of formalin-fixed, paraffin-embedded (FFPE) tissue blocks of the primary and metastatic tumors from our archive of resected specimens using an anti-HMGA2 monoclonal antibody (D1A7, Cell Signaling Technology, Beverly, MA, USA). Staining was enhanced using

an enhancer (Can Get Signal; Toyobo, Tokyo, Japan). Adjacent sections were stained with HE to confirm the histological types. The staining intensity was categorized as –, 1+, 2+, and 3+, and specimens with scores of 2+ or 3+ were defined as "positive." In all specimens, comparisons were made with the staining of normal tissue surrounding the nodules, which was considered negative, as previously reported [36], with a staining intensity of – or 1+. Three investigators independently examined the staining in a blinded manner, and their positive and negative assessments were fully concordant across all specimens.

Statistical analysis

All statistical analyses were conducted using SPSS version 29.0. (IBM, Armonk, NY, USA). Fisher's exact test and Kaplan-Meier analysis with log-rank tests were used to compare the groups and estimate the risk ratios and 95% confidence interval. The level of significance was set at $p < 0.05$.

Ethical considerations

This study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the Certified Review Board of the Dokkyo Medical University Hospital (25100, R-62-18J). The need for informed consent was waived due to the retrospective nature of the study based on "Ethical Guidelines for Medical and Biological Research Involving Human Subjects." The information disclosure documents were shown, and a poster containing items to be disclosed was displayed in our hospital to provide opportunities to disclose this study.

Results

Expression of HMGA2 in thyroid tissues

First, the 26 thyroid samples, including 15 thyroid disease tissues, were stained immunohistochemically with HMGA2. Positive staining was observed in the majority (six of eight) of the malignant tissues (PTC and FTC), and all ATC cases (three of three) showed focal staining of cell nuclei. A case of minimal invasion in the primary FTC with HE and HMGA2 staining is shown in Fig. 1. The capsular invasion stained for HMGA2 while the intra-capsular area did not. In contrast, benign tissues (one FA and three AG) did not demonstrate positive staining (Fig. 2). These findings strongly suggest the involvement of HMGA2 in malignant tumors. HMGA2 expression was observed in malignant tissues, especially in those with high malignant potential.

Expression of HMGA2 in FTC

Based on the aforementioned findings, we conducted a basic study on the sensitivity of HMGA2 staining and IHC in 44 patients diagnosed with FTC using conventional pathological methods. HMGA2 staining of the marginal and invasive regions was observed in 30 of the 44 primary tumor tissues, all of which were selectively located directly under the tumor capsule or in the infiltration area. However, all primary tumors were positive for HMGA2 and stained more diffusely. Overall, staining observed in FTC tumor tissues was considered focal and not diffuse. Moreover, metastatic tissues with FTC in both bone and brain metastasis cases stained for HMGA2 (Fig. 3).

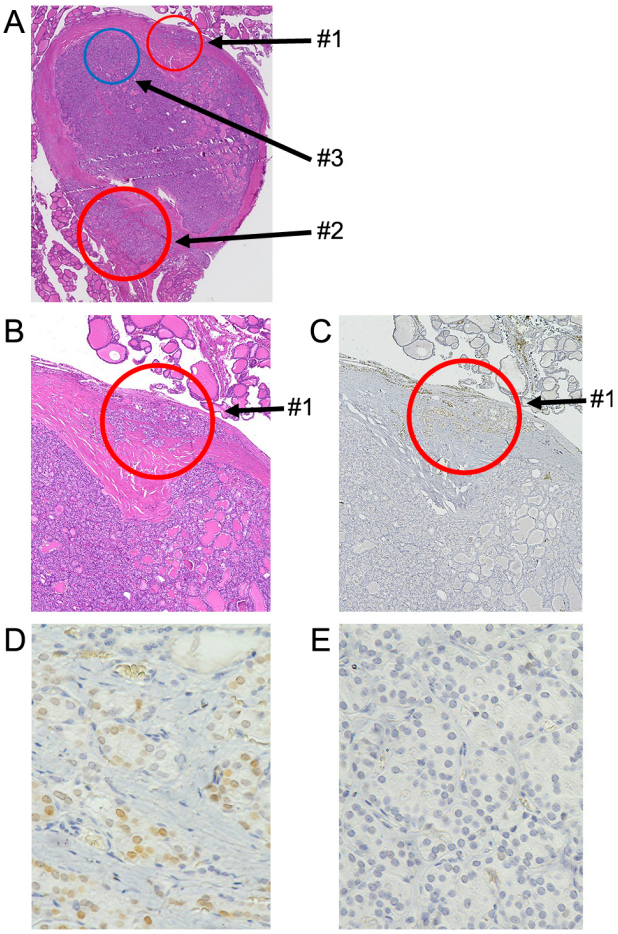


Fig. 1 HE and HMGA2 staining in follicular thyroid carcinoma (FTC). A case of minimal invasion in the primary tissue.
A, capsular invasion (#1, #2) are indicated by red circles and intra-capsular area (#3) are indicated by blue circle (×10 magnification). B and C, marginal area of FTC with capsular invasion stained using HE (B) or HMGA2 (C). B, capsular invasion with HE (#1). C and D, staining of HMGA2 in capsular invasion (#1). C, positive staining of HMGA2 is indicated by red circle. D, the invasive area is shown with positive staining of HMGA2 (×40 magnification). E, negative staining of HMGA2 in the intra-capsular area (#3).

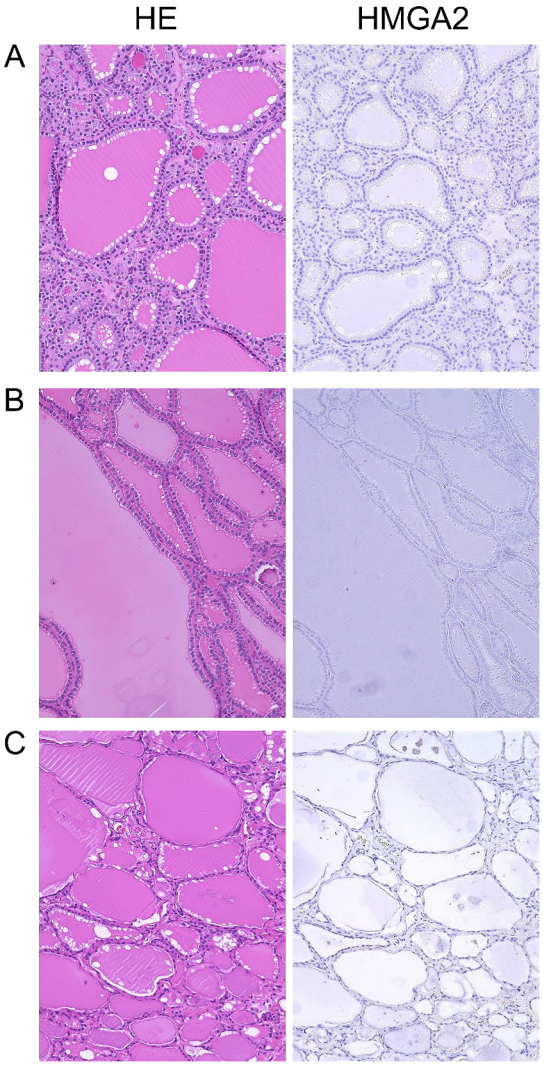


Fig. 2 HE and HMGA2 staining in benign tissues
A, follicular adenoma. B, adenomatous goiter. C, normal tissue.

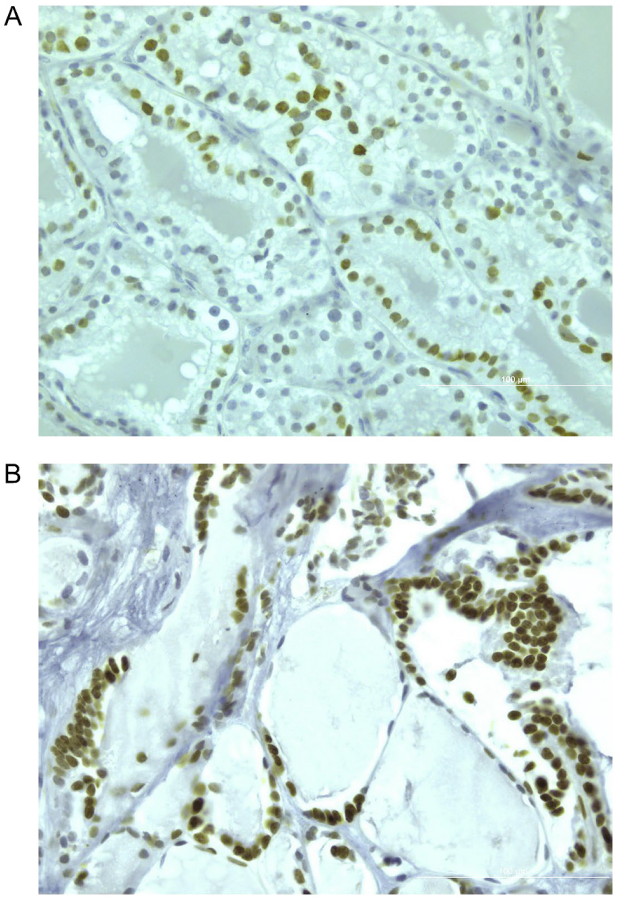


Fig. 3 HMGA2 staining in metastatic tissues with follicular thyroid carcinoma (FTC)
A, a case of bone metastasis. B, a case of brain metastasis.

Characteristics of the study participants

Of the 44 patients examined, 10 developed metastases outside the thyroid gland and experienced thyroid recurrence after surgery. Four patients had distant metastases at the time of initial evaluation. Four patients developed distant metastases to the lung and thyroid recurrences at 1, 2, 12, and 13 years after surgery; one patient developed metastasis to the lung after 6 years of surgery and thyroid recurrence; and one patient developed thyroid recurrence after 10 years of surgery.

The baseline characteristics of the HMGA2-positive and HMGA2-negative groups of the 44 patients (including M1) are shown in Table 1. Patients were divided into two groups according to their age at the time of surgery: <45 and ≥45 years. Tumor size, defined as the maximum diameter of the resected primary tumor recorded in the pathological report, was divided into two groups: ≤4 cm and >4 cm. In addition, we used sex, TNM [pT: T1 (T1a and T1b), T2, T3 (T3a and T3b), T4 (T4a and T4b), pN: LN metastasis, and pM: distant metastasis], capsular invasion, vascular invasion, type of invasion (widely, encapsulated angioinvasive and minimally invasive), and HMGA staining as factors.

Association of positive HMGA2 staining with metastasis and recurrence

Fisher's exact test revealed an association of positive HMGA2 staining with metastasis and recurrence (Table 1). In all patients, the association of positive HMGA2 staining with metastasis and recurrence was found to be significant ($p = 0.018$).

Potential of HMGA2 as a prognostic marker of metastatic recurrence

Baseline characteristics at the primary surgery of metastatic FTC and metastasis-free FTC cases are shown in Table 2. HMGA2 staining (M0) could determine prognosis and presence or absence of metastasis, with a sensitivity of 100%, specificity of 41.2%, positive predictive

Table 1 Baseline characteristics between HMGA2 positive group and HMGA2 negative group

	Overall $N = 44$		HMGA2				p value
			Positive ($N = 30$)		Negative ($N = 14$)		
	N	%	N	%	N	%	
Age							0.738
≥45 yr.	29	65.9	19	63.3	10	71.4	
<45 yr.	15	34.1	11	36.7	4	28.6	
Gender							0.132
Male	11	25.0	5	16.7	6	42.9	
Female	33	75.0	25	83.3	8	57.1	
Size							0.489
>4 cm	29	65.9	11	36.7	3	21.4	
≤4 cm	15	34.1	19	63.3	11	78.6	
pT							0.290
T4 (T4a & T4b)	4	9.1	4	13.3	0	0.0	
T1–T3	40	90.9	26	86.7	14	100.0	
pN							1.000
N1 (N1a & N1b)	5	11.4	4	13.3	1	7.1	
N0	39	88.6	26	86.7	13	92.9	
pM							0.290
M1	4	9.1	4	13.3	0	0.0	
M0	40	90.9	26	86.7	14	100.0	
Capsular Invasion							0.540
(+)	42	95.5	29	96.7	13	92.9	
(–)	2	4.5	1	3.3	1	7.1	
Vascular Invasion							1.000
(+)	27	61.4	18	60.0	9	64.3	
(–)	17	38.6	12	40.0	5	35.7	
Type of Invasion							0.076
Widely	11	25.0	10	33.3	1	7.1	
Encapsulated angioinvasive and Minimally	33	75.0	20	66.7	13	92.9	
Metastatic Recurrence							0.018
+ metastasis	10	22.7	10	33.3	0	0.0	
– metastasis	34	77.3	20	66.7	14	100.0	

value of 23.1%, and negative predictive value of 100%, suggesting its application in the exclusion of metastasis in postoperative diagnosis.

Kaplan-Meier curves with log-rank tests showed an association between positive HMGA2 staining with metastasis and recurrence, but the relationship did not reach statistical significance. Moreover, a significant association of HMGA2 negativity with metastasis and DFS was observed ($p = 0.090$) (Fig. 4). The association of positive HMGA2 staining with metastasis and recurrence was not significant. However, this difference was only marginally significant ($p < 0.10$). Therefore, an association of positive HMGA2 staining with metastasis and recurrence cannot be ruled out. However, further studies are required to confirm this association. Tumor size (>4 cm) and wide invasion were also found to be significant factors ($p = 0.043$, $p < 0.001$, Fig. 4), which was consistent with previous reports.

Estimated risk ratios for metastatic recurrence in patients with FTC

We estimated the risk ratios for metastatic recurrence in patients with FTC with and without HMGA2. The risk ratio without HMGA2 was significantly reduced by 30% compared to that with HMGA2 (95% CI in the group without HMGA2 was 0.395–0.947, Fig. 5).

Table 2 Baseline characteristics at the Primary Surgery between Metastatic FTC and Metastasis-Free FTC

	Overall $N = 40$		Metastatic Recurrence				p value
			Yes ($N = 6$)		No ($N = 34$)		
	N	%	N	%	N	%	
Age							0.615
≥45 yr.	26	65.0	3	50.0	23	67.6	
<45 yr.	14	35.0	3	50.0	11	32.4	
Gender							0.689
Male	9	22.5	1	16.7	9	26.5	
Female	31	77.5	5	83.3	25	73.5	
Size							0.043
>4 cm	12	30.0	4	66.7	8	23.5	
≤4 cm	28	70.0	2	33.3	26	76.5	
pT							0.109
T4 (T4a & T4b)	3	7.5	2	33.3	1	2.9	
T1–T3	37	92.5	4	66.7	33	97.1	
pN							0.878
N1 (N1a & N1b)	3	7.5	1	16.7	2	5.9	
N0	37	92.5	5	83.3	32	94.1	
Capsular Invasion							0.492
(+)	38	95.0	6	100.0	32	94.1	
(–)	2	5.0	0	0.0	2	5.9	
Vascular Invasion							0.914
(+)	24	60.0	4	66.7	20	58.8	
(–)	16	40.0	2	33.3	14	41.2	
Type of Invasion							<0.001
Widely	8	20.0	5	83.3	3	8.8	
Encapsulated angioinvasive and Minimally	32	80.0	1	16.7	31	91.2	
HMGA2							0.090
Positive	26	65.0	6	100.0	20	58.8	
Negative	14	35.0	0	0.0	14	38.2	

Discussion

HMGA2 is involved in the growth and differentiation of stem cells [2] and various malignant tumors, including thyroid cancer. In this study, we found that most differentiated and all undifferentiated carcinomas stained positive for HMGA2, whereas benign diseases stained negative. These findings strongly suggest the involvement of HMGA2 in the pathogenesis of malignant tumors. HMGA2-positive cases exhibited the distribution of positive cells in a focal pattern within the tissue. Therefore, we were able to identify tissues in which even a small portion of strongly positive cells were found. In contrast, in previously reported cases, the positive cells were reported to be diffusely stained in the tumor tissue area. The focal staining pattern obtained in this study may reflect the diversity of cells in the tumor tissue. In the present study, both PTC and undifferentiated carcinoma were positive for HMGA2 staining, which was generally consistent with the positivity rates (67–92%) reported previously. In contrast, some previously reported positive rates (19–56%) were not consistent with those reported in our study [27, 34, 36]. Whether this difference was due to regional or racial differences in patients or due to variations in the judgment of the pathologists in diagnosing FTC [37] remains unclear.

Some previous studies have shown a recurrence-free rate of 100% in patients with FTC after total thyroidectomy [38]. This indicates that aggressive complementary total thyroidectomy or intra-iodine radioiodine therapy, including ablation, could improve the prognosis in patients with these factors. In contrast, we observed longer DFS in HMGA2 staining-negative cases. Risk factors for distant metastases in follicular thyroid cancer include

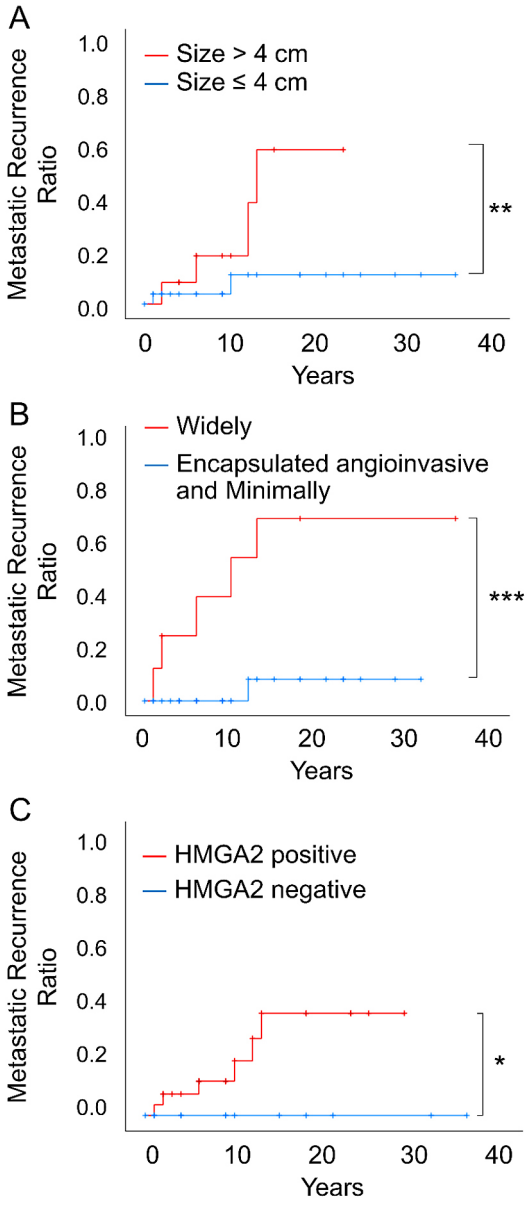


Fig. 4 Cumulative metastatic recurrence ratio of follicular thyroid carcinoma (FTC)

Kaplan-Meier analysis with log-rank test was performed. A, size of primary tumor (p value = 0.043). B, type of Invasion (p value < 0.001). C, HMGA2 staining (p value = 0.090). * $p < 0.1$, ** $p < 0.05$, *** $p < 0.001$.

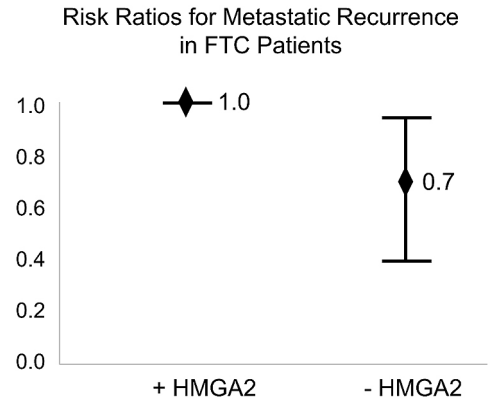


Fig. 5 Estimated risk ratios for metastatic recurrence in patients with follicular thyroid carcinoma (FTC) with or without HMGA2

95% CI of the group without HMGA2 was 0.395–0.947.

HMGA2 positivity, tumor size (>4 cm), and wide invasion. Patients with these factors should be followed up, and their prognoses require further investigation.

The use of HMGA2 as a diagnostic marker has already been investigated using reverse transcription polymerase chain reaction (RT-PCR) in Europe and the United States [23, 27, 39, 40]. According to these studies, the frequency of HMGA2 mRNA overexpression in different types of thyroid cancer was 77–96% in PTC, 81–90% in FTC, and 67–100% in undifferentiated carcinoma. Moreover, the overexpression found using RT-PCR was generally higher than that observed using IHC. Although the sensitivity of detection was probably amplified by PCR, the superior capacity of IHC could easily demonstrate that tissue heterogeneity remains unchanged during detailed pathological examinations.

Our study had a few limitations that need consideration. First, patients with M1 disease at the initial examination were included. Therefore, reverse causation cannot be ruled out. However, the possibility of reverse causation may be minimal because the difference in phi coefficients between all participants and those with M0 was slight. Second, since the sample size was limited, our findings cannot be generalized. Future studies with larger sample sizes are required to validate our study findings.

Conclusion

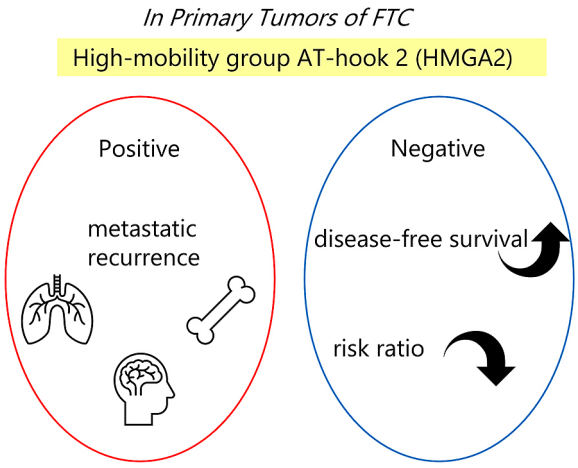
Positive IHC staining for HMGA2 in primary tumors can be used to predict the prognosis and detect prognostic factors in malignant thyroid tumors associated with metastatic recurrence in FTC (Graphical Abstract).

Acknowledgments

The authors would like to express gratitude to Dr. M. Hirokawa for providing the pathological specimens (Kuma Hospital, Kobe, Hyogo, Japan).

Conflict of Interest Statement

The authors declare no conflicts of interest.



Graphical Abstract

Funding

This study was supported by a Research Incentive Grant from Dokkyo Medical University [Grant Number 00002269] and JSPS KAKENHI [Grant Number 26460653]. The funding organization had no role in the design or conduct of this study.

Disclosure

T.K. is a member of *Endocrine Journal*'s Editorial Board.

References

1. Frost L, Baez MA, Harrilal C, Garabedian A, Fernandez-Lima F, *et al.* (2015) The dimerization state of the Mammalian High Mobility Group Protein AT-Hook 2 (HMGA2). *PLoS One* 10: e0130478.
2. Mansoori B, Mohammadi A, Ditzel HJ, Duijf PHG, Khaze V, *et al.* (2021) HMGA2 as a critical regulator in cancer development. *Genes (Basel)* 12: 269.
3. Kalluri R, Weinberg RA (2009) The basics of epithelial-mesenchymal transition. *J Clin Invest* 119: 1420–1428.
4. Fusco A, Fedele M (2007) Roles of HMGA proteins in cancer. *Nat Rev Cancer* 7: 899–910.
5. Morishita A, Zaidi MR, Mitoro A, Sankarasharma D, Szabolcs M, *et al.* (2013) HMGA2 is a driver of tumor metastasis. *Cancer Res* 73: 4289–4299.
6. Takahashi T, Kawaji H, Murakawa Y, Hayashizaki Y, Murakami T, *et al.* (2021) Significance of HMGA2 expression as independent poor prognostic marker in perihilar and distal cholangiocarcinoma resected with curative intent. *Eur J Surg Oncol* 47: 394–400.
7. Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, *et al.* (2022) Overview of the 2022 WHO classification of thyroid neoplasms. *Endocr Pathol* 33: 27–63.
8. Passler C, Scheuba C, Prager G, Kaczirek K, Kaserer K, *et al.* (2004) Prognostic factors of papillary and follicular thyroid cancer: differences in an iodine-replete endemic goiter region. *Endocr Relat Cancer* 11: 131–139.
9. Su DH, Chang TC, Chang SH (2019) Prognostic factors on outcomes of follicular thyroid cancer. *J Formos Med Assoc* 118: 1144–1153.
10. Yamazaki H, Sugino K, Katoh R, Matsuzu K, Masaki C, *et al.* (2021) Outcomes for minimally invasive follicular thyroid carcinoma in relation to the change in age stratification in the AJCC 8th edition. *Ann Surg Oncol* 28: 3576–3583.
11. Sugino K, Ito K, Nagahama M, Kitagawa W, Shibuya H, *et al.* (2011) Prognosis and prognostic factors for distant metastases and tumor mortality in follicular thyroid carcinoma. *Thyroid* 21: 751–757.
12. Sugino K, Kameyama K, Ito K, Nagahama M, Kitagawa W, *et al.* (2012) Outcomes and prognostic factors of 251 patients with minimally invasive follicular thyroid carcinoma. *Thyroid* 22: 798–804.
13. Stenson G, Nilsson IL, Mu N, Larsson C, Lundgren CI, *et al.* (2016) Minimally invasive follicular thyroid carcinomas: prognostic factors. *Endocrine* 53: 505–511.
14. Zidan J, Kassem S, Kuten A (2000) Follicular carcinoma of the thyroid gland: prognostic factors, treatment, and survival. *Am J Clin Oncol* 23: 1–5.
15. Ito Y, Miyauchi A, Hirokawa M, Yamamoto M, Oda H, *et al.* (2018) Prognostic value of the 8th edition of the tumor-node-metastasis classification for patients with papillary thyroid carcinoma: a single-institution study at a high-volume center in Japan. *Endocr J* 65: 707–716.
16. Ito Y, Hirokawa M, Higashiyama T, Takamura Y, Miya A, *et al.* (2007) Prognosis and prognostic factors of follicular carcinoma in Japan: importance of postoperative

pathological examination. *World J Surg* 31: 1417–1424.
17. Ito Y, Hirokawa M, Masuoka H, Yabuta T, Kihara M, *et al.* (2013) Prognostic factors of minimally invasive follicular thyroid carcinoma: extensive vascular invasion significantly affects patient prognosis. *Endocr J* 60: 637–642.
18. Ito Y, Miyauchi A, Tomoda C, Hirokawa M, Kobayashi K, *et al.* (2014) Prognostic significance of patient age in minimally and widely invasive follicular thyroid carcinoma: investigation of three age groups. *Endocr J* 61: 265–271.
19. O'Neill CJ, Vaughan L, Learoyd DL, Sidhu SB, Delbridge LW, *et al.* (2011) Management of follicular thyroid carcinoma should be individualised based on degree of capsular and vascular invasion. *Eur J Surg Oncol* 37: 181–185.
20. Podda M, Saba A, Porru F, Reccia I, Pisanu A (2015) Follicular thyroid carcinoma: differences in clinical relevance between minimally invasive and widely invasive tumors. *World J Surg Oncol* 13: 193.
21. Asari R, Koperek O, Scheuba C, Riss P, Kaserer K, *et al.* (2009) Follicular thyroid carcinoma in an iodine-replete endemic goiter region: a prospectively collected, retrospectively analyzed clinical trial. *Ann Surg* 249: 1023–1031.
22. Ito Y, Hirokawa M, Masuoka H, Yabuta T, Fukushima M, *et al.* (2013) Distant metastasis at diagnosis and large tumor size are significant prognostic factors of widely invasive follicular thyroid carcinoma. *Endocr J* 60: 829–833.
23. Lappinga PJ, Kip NS, Jin L, Lloyd RV, Henry MR, *et al.* (2010) HMGA2 gene expression analysis performed on cytologic smears to distinguish benign from malignant thyroid nodules. *Cancer Cytopathol* 118: 287–297.
24. Kim BH, Kim SJ, Kim M, Lee SW, Jeong SY, *et al.* (2018) Diagnostic performance of HMGA2 gene expression for differentiation of malignant thyroid nodules: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 89: 856–862.
25. Rodrigues R, Roque L, Espadinha C, Pinto A, Domingues R, *et al.* (2007) Comparative genomic hybridization, BRAF, RAS, RET, and oligo-array analysis in aneuploid papillary thyroid carcinomas. *Oncol Rep* 18: 917–926.
26. Titov SE, Ivanov MK, Demenkov PS, Katanyan GA, Kozorezova ES, *et al.* (2019) Combined quantitation of HMGA2 mRNA, microRNAs, and mitochondrial-DNA content enables the identification and typing of thyroid tumors in fine-needle aspiration smears. *BMC Cancer* 19: 1010.
27. Chiappetta G, Ferraro A, Vuttariello E, Monaco M, Galdiero F, *et al.* (2008) HMGA2 mRNA expression correlates with the malignant phenotype in human thyroid neoplasias. *Eur J Cancer* 44: 1015–1021.
28. Mayr C, Hemann MT, Bartel DP (2007) Disrupting the pairing between let-7 and Hmga2 enhances oncogenic transformation. *Science* 315: 1576–1579.
29. Vasko V, Espinosa AV, Scouten W, He H, Auer H, *et al.* (2007) Gene expression and functional evidence of epithelial-to-mesenchymal transition in papillary thyroid carcinoma invasion. *Proc Natl Acad Sci U S A* 104: 2803–2808.
30. Lloyd RV, Buehler D, Khanafshar E (2011) Papillary thyroid carcinoma variants. *Head Neck Pathol* 5: 51–56.
31. Qiu K, Xie Q, Jiang S, Lin T (2020) miR-98-5p promotes apoptosis and inhibits migration and cell growth in papillary thyroid carcinoma through Bax/Caspase-3 by HMGA2. *J Clin Lab Anal* 34: e23044.
32. Rice SJ, Lai SC, Wood LW, Helsley KR, Runkle EA, *et al.* (2013) MicroRNA-33a mediates the regulation of high mobility group AT-hook 2 gene (HMGA2) by thyroid transcription factor 1 (TTF-1/NKX2-1). *J Biol Chem* 288: 16348–16360.
33. Ding C, Shi T, Wu G, Man J, Han H, *et al.* (2022) The anti-cancer role of microRNA-143 in papillary thyroid carcinoma by targeting high mobility group AT-hook 2. *Bioengineered* 13: 6629–6640.
34. Jang MH, Jung KC, Min HS (2015) The diagnostic usefulness of HMGA2, survivin, CEACAM6, and SFN/14-3-3 δ in follicular thyroid carcinoma. *J Pathol Transl Med* 49: 112–117.
35. Li H, Zhao L, Zhang Z, Zhang H, Ding C, *et al.* (2017) Roles of microRNA let-7b in papillary thyroid carcinoma by regulating HMGA2. *Tumour Biol* 39: 1010428317719274.
36. Prasad NB, Kowalski J, Tsai HL, Talbot K, Somervell H, *et al.* (2012) Three-gene molecular diagnostic model for thyroid cancer. *Thyroid* 22: 275–284.
37. Hirokawa M, Carney JA, Goellner JR, DeLellis RA, Heffess CS, *et al.* (2002) Observer variation of encapsulated follicular lesions of the thyroid gland. *Am J Surg Pathol* 26: 1508–1514.
38. Lo CY, Chan WF, Lam KY, Wan KY (2005) Follicular thyroid carcinoma: the role of histology and staging systems in predicting survival. *Ann Surg* 242: 708–715.
39. Jin L, Lloyd RV, Henry MR, Erickson LA, Sebo TJ, *et al.* (2015) The diagnostic utility of combination of HMGA2 and IMP3 qRT-PCR testing in thyroid neoplasms. *Appl Immunohistochem Mol Morphol* 23: 36–43.
40. Belge G, Meyer A, Klemke M, Burchardt K, Stern C, *et al.* (2008) Upregulation of HMGA2 in thyroid carcinomas: a novel molecular marker to distinguish between benign and malignant follicular neoplasias. *Genes Chromosomes Cancer* 47: 56–63.