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Expression and prognostic significance of melatonin receptor MT1 in patients with gastric adenocarcinoma

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Melatonin receptor type 1 (MTNR1A or MT1) is known to play an important role in cancer progression; however, its prognostic value for resected gastric adenocarcinoma (RGA) is unknown. In this study, we examined the potential of MT1 as a prognostic biomarker for RGA. The expression of the MT1 was evaluated in 67 patients with RGA by immunohistochemistry, and the relationship between MT1 levels and RGA prognosis was analyzed by Chi-square test, multivariate Cox regression, Kaplan-Meier method, and log-rank test. High MT1 expression was associated with a poor survival rate (29.0%, p=0.002) and the occurrence of metastasis (62.9%, p=0.004). Kaplan-Meier survival analysis and log rank tests revealed that patients with high expression of the MT1 had significantly shorter median overall survival compared to those with low expression (33.0 vs. 65.0 months, respectively; p=0.02). Multivariate Cox analysis indicated that the calculated death risk (hazard ratio [HR]) in patients with high expression levels of the MT1 increased to 2.68 (95% confidence interval [CI] 1.21–5.94, p=0.015), which was higher compared to those with low levels. HR of death was also high in patients with advanced T stage (2.51; 95 % CI 1.00–6.26, p=0.049) and metastasis (5.02; 95% CI 1.94–13.03, p=0.001). Our results showed that high MT1 expression in primary gastric adenocarcinoma tissues was associated with the occurrence of metastasis and poor prognosis. It may have prognostic significance as a potential biomarker in patients with RGA.

Key words: melatonin receptor, resected gastric adenocarcinoma, immunohistochemistry, prognosis, metastasis

Gastric cancer is one of the most common digestive tract malignancies worldwide [1], and gastric adenocarcinoma (GA) represents over 90% of gastric tumors. Surgery combined with postoperative chemotherapy is still the most effective method for treating resectable GA (RGA), but the prognosis remains grim in patients with late-stage cancer. Therefore, early detection and timely treatment are particularly important for increasing the survival rate. In this regard, molecular prognostic biomarkers specific for early-stage GA are of great clinical value, as they can direct therapeutic approaches and, ultimately, extend patient's survival [2].

Melatonin is a hormone produced mainly in the pineal gland as well as in the gastrointestinal tract, retina, skin, bone marrow, and reproductive organs [3–5]. Enterochromaffin cells of the gastrointestinal mucosa are the main source of melatonin outside the pineal gland [6], and a previous study suggested that melatonin could affect the function of the gastrointestinal epithelium and smooth muscles as well as of lymphatic tissues of the immune system [7]. Furthermore, it has been shown that melatonin can inhibit the growth of gastric tumors through its immunomodulatory and antioxidant activities, stimulation of apoptosis, and inhibition of angiogenesis [8, 9].

The pleiotropic effects of melatonin are mediated by both receptor-independent and receptor-dependent mechanisms [10–12]. Melatonin-specific membrane receptors belong to the G-protein-coupled receptor superfamily [13, 14] and there are two main types of such receptors in humans: MT1 and MT2 (formerly known as MTNR1A and MTNR1B, respectively), which have distinct molecular and functional characteristics [15, 16]. Thus, MT1 is involved in reproduction, metabolism, vasoconstriction, and tumor cell proliferation, whereas MT2 regulates circadian rhythm, vasodilation, and immune responses [17–19]. Activation of MT1 in tumor cells was shown to reduce the production of cyclic

adenosine monophosphate (cAMP), leading to downregulation of protein kinase A (PKA) and decrease in phosphorylation-dependent activation of cAMP response element-binding (CREB) transcription factor [20], which suppressed the growth of cancer cells. Thus, an *in vitro* study indicated that melatonin reduced the proliferation and viability of HepG2 cells by activating p38, ERK, and JNK protein kinases through MT1 receptor [12]. Another study revealed that melatonin-MT1 signaling was involved in suppression of breast cancer cell invasion, possibly through downregulation of the p38 pathway and inhibition of the expression and activity of metalloproteinases MMP-2 and MMP-9 [21]. Importantly, Nasrabadi et al. [22, 23] found that the mRNA expression of MT1 and MT2 in tumors and marginal cancer tissues was increased in GA patients compared with healthy individuals; however, these studies did not evaluate MT1 and MT2 protein expression in GA.

Given the expression of MT1 in the gastrointestinal tract and anticancer effects of melatonin-MT1 signaling, we hypothesized that MT1 levels in RGA may predict patient's outcome. Therefore, the aim of this study was to examine MT1 expression in RGA and evaluate its potential as an early-stage cancer biomarker for patients with RGA.

Table 1. Patients' characteristics.

Variable	Cases (n=67)	
	n	%
Age		
<60	34	50.7
≥60	33	49.3
Gender		
Male	47	70.1
Female	20	29.9
Gross findings		
Apophysis	12	17.9
Invasion	55	82.1
Tumor site		
Proximal/Mid	31	46.3
Distal	36	53.7
Lymph node metastasis		
No metastasis	32	47.8
Metastasis	35	52.2
T stage		
T1+T2	24	35.8
T3+T4	43	64.2
Survival		
Alive	33	49.3
Dead	34	50.7
MT1 expression		
Low	36	53.7
High	31	46.3

Patients and methods

Patients. This retrospective study involved 67 patients with the pathological diagnosis of primary GA, who underwent surgery between 2006 and 2009 at the Fujian Medical University Union Hospital (Fuzhou, China). The patients had no additional cancers, such as osteosarcoma, breast cancer, or other diseases accompanied by high expression of the MT1; they were followed up every six months, beginning at three months after operation until December 2014. Clinical data, including age, gender, tumor site, gross findings, T stage, and lymph node metastasis were obtained from detailed electronic medical records. The tumor tissues were taken from the resected primary tumors and the survival data were collected through telephone and the Social Security Death Index. This research was approved by the Ethics Committee of Fujian Medical University Union Hospital (2018KY062).

Immunohistochemistry. The expression of the MT1 was analyzed in paraffin-embedded RGA tissues by immunohistochemistry (IHC) using a rabbit anti-human MT1 polyclonal antibody (1:100 dilution; CUSABIO, Wuhan, China) as described in our previous study [24]. The immunohistochemical staining results were assigned a mean score taking into account both the intensity of staining and the proportion of tumor cells with an unequivocal positive reaction. Each section was independently assessed by two pathologists blind to the clinical information in the experiment. The results were scored as 0, 1, 2, and 3 based on staining intensity and scope: scores 0 or 1 were regarded as low expression and 2 or 3 as high expression of the MT1 [25].

Statistical analysis. The experimental data were analyzed using the SPSS17.0 software (SPSS Inc., Chicago, IL, USA). Chi-square test was performed to determine the association of MT1 receptor expression with clinicopathological features and prognosis of patients. The correlation between MT1 expression and patient survival was further evaluated by univariate and multivariate Cox regression analysis, Kaplan-Meier estimator, and log-rank test. In addition, the multivariate Cox regression model was adjusted for age, gender, tumor site, gross findings, T stage, and lymph node metastasis. All tests were two-sided, and $p<0.05$ was considered as statistically significant.

Results

Patient characteristics. The characteristics and clinical information for the 67 patients with primary GA were shown in Table 1. There were 47 men (70.1%) and 20 women (29.9%); 34 patients were <60 years old, and 33 were ≥60 years old (median, 59 years; range, 37.0–88.0 years). Among the patients, 24 (35.8%) had T1 or T2 stages and 43 (64.2%) had T3 or T4 stages. Thirty-four patients (50.7%) died during the follow-up period; the median follow-up time was 57 months and the median overall survival was 60 months (range, 2.0–104.0 months).

Relationship between MT1 expression and clinical characteristics. Among the 67 RGA tissue specimens examined by IHC, 31 (46.3%) had high MT1 expression (Table 1). As shown in Table 2, MT1 levels were significantly associated with metastasis (p=0.04) and patient survival (p=0.002). Thus, among 35 patients with metastasis and 22 patients with shorter survival, the percentage of those with high MT1 expression in RGA increased to 62.9% and 64.7%, respectively. There was no significant association between MT1 expression and other clinicopathological factors, including age, gender, tumor site, gross findings, and T stage (Table 2). Representative IHC results for tissues with low and high MT1 levels are shown in Figure 1.

Association of MT1 expression with survival. Data analysis with Chi-square tests indicated that high MT1 expression was significantly associated with a poorer survival rate (29.0%, p=0.002) (Table 3). Decreased survival was also correlated with advanced T stage (37.2%, p=0.008) and metastasis (20.0%, p<0.001). Kaplan-Meier survival curves and log-rank tests also indicated that patients with high MT1 levels had significantly shorter median overall survival compared to those with low MT1 levels (33.0 vs. 65.0 months, respectively; p=0.02, Figure 2). Then we further performed the stratified analysis according to metastasis (Figure 3), we found that patients with high expression of MT1 exhibited a shorter survival time (48.0 vs. 70.0 months, p=0.01) in non-metastatic patients (Figure 3A); while in the metastatic patients, no significant relevance was found between MT1 expression and survival time (Figure 3B). Univariate and multivariate Cox regression analyses confirmed these results by showing that positive lymph node metastasis, advanced T stage, and high MT1 expression were significantly associated with an increased risk of death (Table 4). Thus, the calculated death risk (hazard ratio [HR]) in patients with high MT1 expression increased to 2.68 (95%, confidence interval [CI] 1.21–5.94, p=0.015), which was higher compared to that of patients with low MT1 expression. The HR of death was also elevated in patients with advanced T stage and metastasis to 2.51 (95%, CI 1.00–6.26, p=0.049) and 5.04 (95%, CI 1.94–13.03, p=0.001), respectively.

Table 2. Association between MT1 expression and characteristics of patients.

Characteristics	MT1 expression		p-value
	Low (%)	High (%)	
Age			
<60	19 (55.9)	15 (44.1)	0.720
≥60	17 (51.5)	16 (48.5)	
Gender			
Male	24 (51.1)	23 (48.9)	0.502
Female	12 (60.0)	8 (40.0)	
Gross findings			
Apophysis	7 (58.3)	5 (41.7)	0.724
Invasion	29 (52.7)	26 (47.3)	
Tumor site			
Proximal/Mid	15 (48.4)	16 (51.6)	0.416
Distal	21 (58.3)	15 (41.7)	
Lymph node metastasis			
No metastasis	23 (71.9)	9 (28.1)	**0.004***
Metastasis	13 (37.1)	22 (62.9)	
T stage			
T1+ T2	12 (50.0)	12 (50.0)	0.647
T3 + T4	24 (55.8)	19 (44.2)	
Survival			
Alive	24 (72.7)	9 (27.3)	**0.002***
Dead	12 (35.3)	22 (64.7)	

*Statistically significant (p<0.05). MT1, melatonin receptor type 1

Table 3. Association between survival and characteristics of patients

Characteristics	Survival		p-value
	Alive (%)	Deceased %)	
Age			
<60	18 (52.9)	16 (47.1)	0.540
≥60	15 (45.5)	18 (54.5)	
Gender			
Male	24 (51.1)	23 (48.9)	0.650
Female	9 (45.0)	11 (55.0)	
Gross findings			
Apophysis	7 (58.3)	5 (41.7)	0.487
Invasion	26 (47.3)	29 (52.7)	
Tumor site			
Proximal/Mid	15 (48.4)	16 (51.6)	0.895
Distal	18 (50.0)	18 (50.0)	
Lymph node metastasis			
No metastasis	26 (81.3)	6 (18.7)	<
Metastasis	7 (20.0)	28 (80.0)	**0.001***
T stage			
T1+T2	17 (70.8)	7 (29.2)	**0.008***
T3+T4	16 (37.2)	27 (62.8)	
MT1 expression			
Low	24 (66.7)	12 (33.3)	**0.002***
High	9 (29.0)	22 (71.0)	

*Statistically significant (p<0.05). MT1, melatonin receptor type 1

Discussion

The purpose of this study was to investigate MT1 expression, its relationship with clinicopathological characteristics of patients with primary GA, and the potential of MT1 as a biomarker for early-stage GA. Previous studies have confirmed that both MT1 and MT2 are involved in the anticancer effect of melatonin, suggesting that melatonin or melatonin receptor agonists may be used in the treatment of cancer [4, 26]. Nasrabadi et al. [23] demonstrated that MT1 levels were increased in tumor and non-tumor (marginal) tissues of GA patients compared with those in healthy individuals and suggested that the observed upregulation of MT1 surface expression represented a defense mechanism

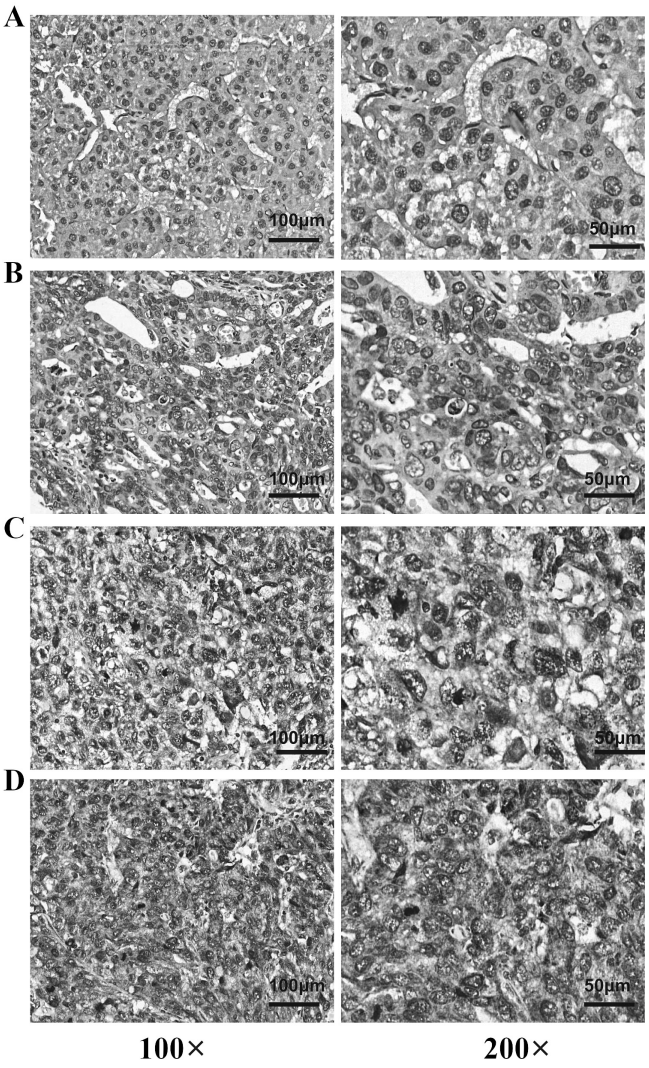

Figure 1. Representative images of MT1 staining in resected gastric adenocarcinoma (RGA). RGA tissue specimens were analyzed by IHC using anti-MT1 antibody and scored according to MT1 staining intensity. A) score '0' for MT1 staining in RGA tissues; B) score '1' for MT1 staining in RGA tissues; C) score '2' for MT1 staining in RGA tissues; D) score '3' for MT1 staining in RGA tissues.

in response to a decrease of melatonin concentration in surrounding tissues. Furthermore, their results indicated that melatonin, through the MT1 receptor, could play a preventive role in GA, especially for patients over 50 years old.

Our current study revealed that high expression of the MT1 was associated with poor prognosis and the occurrence of metastasis in patients with primary GA but did not show significant correlation with other clinicopathological factors. These findings indicated that high levels of MT1 expression were correlated with gastric cancer aggressiveness, which may be linked to tumor cell proliferation [17]. It is known that the secretion of melatonin in healthy people gradually decreases with age [27] and negatively correlates with the expression of the MT1 [28]. Furthermore, serum melatonin

Table 4. Univariate and multivariate Cox regression analyses for overall survival in patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age				
<60	1.00	0.254	1.00	0.063
≥60	1.49 (0.75–2.96)		2.01 (0.96–4.18)	
Gender				
Male	1.00	0.485	1.00	0.107
Female	1.30 (0.63–2.67)		1.94 (0.87–4.35)	
Gross findings				
Apophysis	1.00	0.651	1.00	0.736
Invasion	1.25 (0.48–3.23)		1.18 (0.45–3.10)	
Tumor site				
Proximal/Mid	1.00	0.922	1.00	0.473
Distal	1.03 (0.53–2.03)		0.76 (0.36–1.60)	
Lymph node metastasis				
No metastasis	1.00	**<0.001***	1.00	**0.001***
Metastasis	6.60 (2.71–16.09)		5.02 (1.94–13.03)	
T stage				
T1+T2	1.00	**0.018***	1.00	**0.049***
T3+T4	2.75 (1.20–6.37)		2.51 (1.00–6.26)	
MT1 expression				
Low	1.00	**0.003***	1.00	**0.015***
High	2.91 (1.43–5.94)		2.68 (1.21–5.94)	

*Statistically significant (p<0.05). HR, hazard ratio; CI, confidence interval; MT1, melatonin receptor type 1.

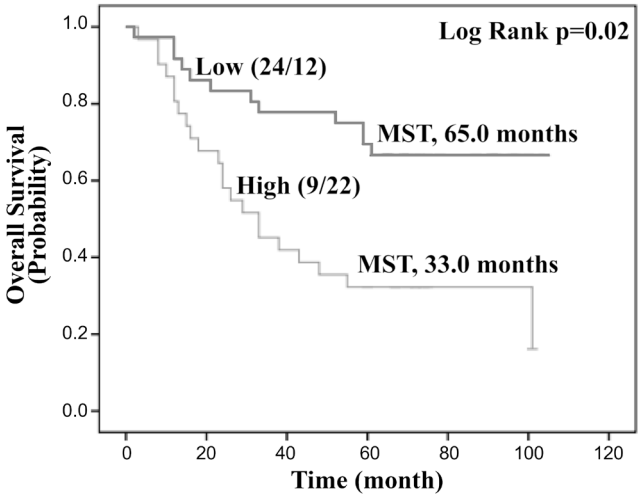

Figure 2. Kaplan-Meier curves according to MT1 expression levels in RGA samples of 67 patients. MST, median survival time (months); p=0.02 by log-rank test.

levels were found to be significantly lower in ovarian cancer patients compared to those in healthy women [28]. Therefore, the correlation of high MT1 expression with poor prognosis observed in this study may be because the level of melatonin in patients with tumor metastasis was extremely low, and

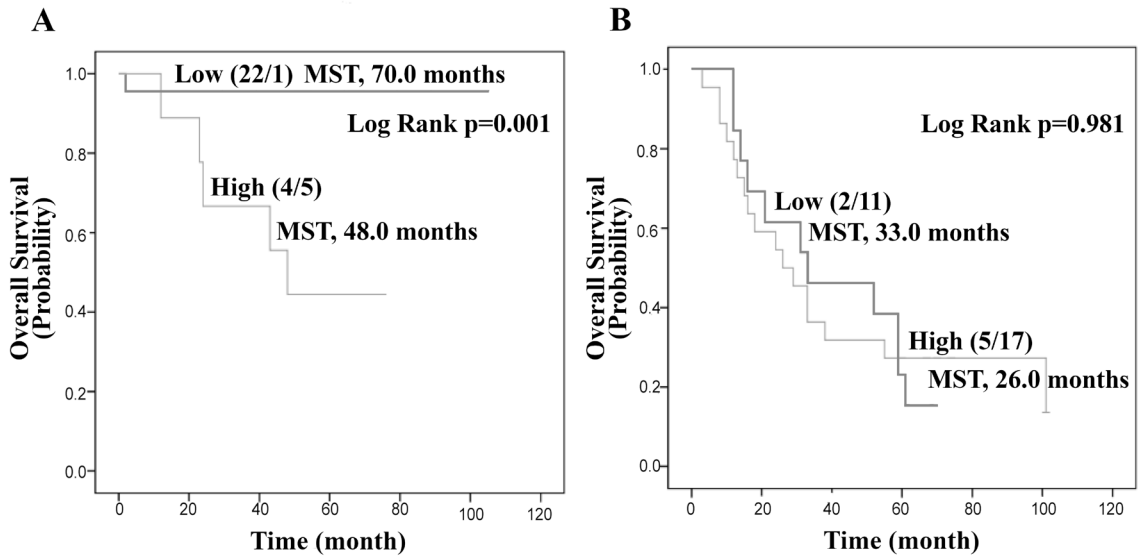

Figure 3. The stratified analysis according to metastasis in RGA samples of 67 patients. A) Kaplan-Meier curves according to MT1 receptor expression levels without metastasis patients; B) Kaplan-Meier curves according to MT1 receptor expression levels with metastasis patients. MST, median survival time (months).

the feedback caused the increase of MT1, which leaded to excessive accumulation of MT1 on the membrane of GA cells. This hypothesis provides a basis for clinical research on the application of exogenous melatonin in the treatment of gastric cancer. Hence, a previous clinical study has already shown that GA patients receiving combination treatment with chemotherapeutic drugs and melatonin had significantly higher rates of overall tumor regression and 2-extra-year survival than those receiving chemotherapy alone [29].

In conclusion, this is the first study to demonstrate that high MT1 expression in primary GA tissues was related to the occurrence of metastasis and poor prognosis, as indicated by shorter survival time and increased death risk. Our results suggest that the expression of the MT1 can be a candidate for independent prognostic biomarker in patients with RGA.

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