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Original Research

Clinical significance of MET receptor protein and mRNA expression in invasive breast cancer

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Summary

Mesenchymal epithelial transition (MET) receptor factor, the hepatocyte growth factor receptor, is a receptor tyrosine kinase that is overexpressed and activated in a subset of human epithelial malignancies. In this study, the clinical significance of mesenchymal epithelial transition protein and mRNA expression in invasive breast cancer tissues was investigated. A tissue microarray was constructed using tissues from 371 patients with invasive ductal cancer (IDC) who underwent radical tumor excision for breast cancer. The correlation between mesenchymal epithelial transition mRNA and protein expression were analyzed with mesenchymal epithelial transition immunohistochemistry (IHC) and RNAscope *in situ* hybridization (ISH). Positive immunohistochemistry results for mesenchymal epithelial transition protein were detected in 46 (13%) patients, and 45 (12%) patients exhibited high mesenchymal epithelial transition mRNA levels. High mesenchymal epithelial transition protein and high mesenchymal epithelial transition mRNA levels were significantly associated with high histologic grade, negative estrogen receptor (ER) status, and a high proliferation index in invasive ductal cancer. Kaplan-Meier analysis showed no significant association of either mesenchymal epithelial transition mRNA or protein expression with survival. There was, however, a significant correlation between mesenchymal epithelial transition mRNA expression and mesenchymal epithelial transition protein expression. The present study showed that mesenchymal epithelial transition mRNA and protein expression are significantly correlated and are important prognostic factors in invasive breast cancer.

Key words: Immunohistochemistry; *In situ* hybridization; Invasive ductal carcinoma; MET.

Introduction

Breast cancer is the most common cancer among women worldwide [1]. Epidemiological studies have shown that more than 400,000 individuals worldwide die each year from breast cancer [2]. Mesenchymal epithelial transition receptor factor (hereafter, referred to as MET) is a plasma membrane protein that transduces signals from the extracellular matrix to the cytoplasm and is activated by the binding of hepatocyte growth factor (HGF, also known as scatter factor) [3]. The *MET* proto-oncogene is located on chromosome 7q31 and encodes a receptor tyrosine kinase (RTK) that acts as the receptor for HGF. *MET* gene mutation, overexpression, and amplification occur in a variety of human tumor types, and these events are closely related to the aberrant activation of the HGF/MET signaling pathway [4]. Overexpression of MET has been shown to contribute to the development of invasive phenotypes during breast cancer progression both *in vivo* and *in vitro*. Some studies found MET to act as a negative prognostic biomarker and predict poor survival in breast cancer patients [5-7]. Although some studies suggest that MET is a stronger indicator of poor prognosis than traditional markers, such as HER2/neu and epidermal growth factor receptor (EGFR) [5, 8, 9], other studies suggest there is no statistically significant relation between MET and breast cancer prognosis [8, 10, 11]. In recent years, MET was reported to be associated with a favorable prognosis in breast cancer patients [12, 13]. However, MET was also found to play a role in the development of herceptin and endocrine therapy-resistance in breast cancer [6, 7]. In breast cancer studies, MET protein overexpression determined using immunohistochemistry (IHC) was 3.8–80.0%, *MET* gene copy number gain determined using quantitative real-time polymerase chain reaction (qPCR) was 44–74.2%, and *MET* gene amplification determined using fluorescence *in situ* hybridization (FISH) was 4.7–27.7% [14]. Of these methods, IHC is widely used in clinical practice and is the most common screening method for MET-positive cancers.

In this study, RNA *in situ* hybridization (ISH) was performed using paired DNA oligonucleotide probes and preamplifier, amplifier-labeled probes for visualization [15]. Quantification of MET protein levels (by IHC) and *MET* mRNA levels (by RNAscope ISH) was also carried out for 371 invasive breast cancer tissues.

Materials and Methods

Surgically resected breast cancer tissue specimens obtained from 371 patients who underwent mastectomy for invasive ductal carcinoma (IDC) at Kangbuk Samsung Hospital (Seoul, Korea) from March 2003 to December 2007,

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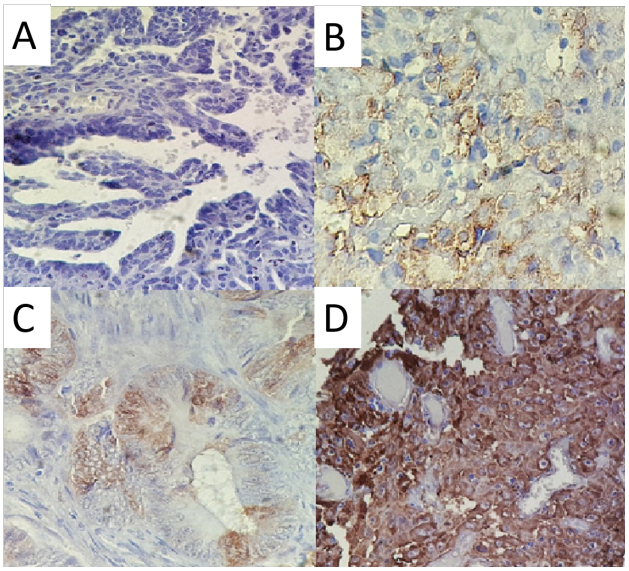

Figure 1. Representative images for MET immunohistochemistry (IHC). (A) IHC score 0, (B) IHC score 1, (C) IHC score 2, and (D) IHC score 3 (400×).

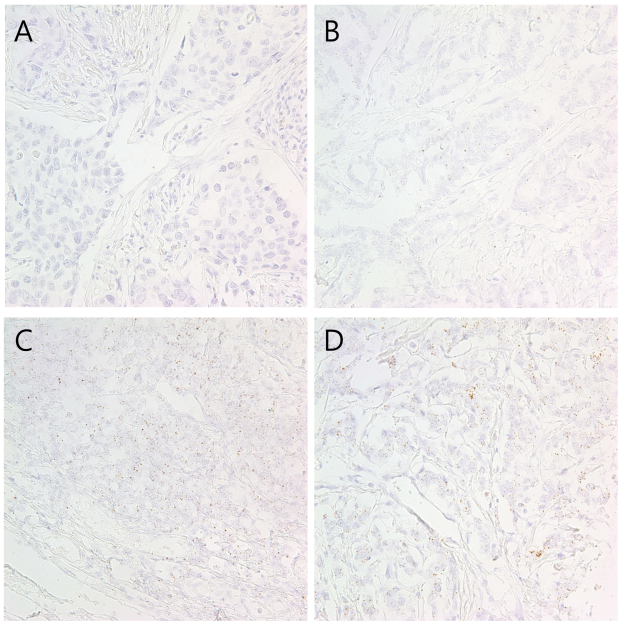

Figure 2. Representative images for MET RNA in situ hybridization (ISH). (A) ISH score 0, (B) ISH score 1, (C) ISH score 2, and (D) ISH score 3 (400×).

were collected. The submitted study followed the guidelines of and was approved by the local institutional review board (KBC14077). Patient survival data, including dates and causes of death, were obtained from the Korean Central Cancer Registry, Ministry of Health and Welfare, Korea. Standard histopathological examination included the type of cancer and the pathological tumor stage, assessed according to the criteria reported in the sixth edition of the AJCC Staging Manual [16].

Tissue array blocks were prepared and *in situ* detection of *MET* mRNA was performed manually using an RNAscope kit, according to the manufacturer's instructions. Briefly, formalin-fixed, paraffin-embedded (FFPE) tissue sections (4 μm thick) were pretreated by heating and incubating with proteases prior to hybridization with *MET* target probes. Positive staining was indicated by brown punctate dots present in the nucleus and/or cytoplasm. *MET* expression levels were categorized into five grades according to the manufacturer's scoring guidelines: no staining (score 0), staining that was difficult to see at a 40 × magnification in more than 10% of tumor cells (score 1), staining that was difficult to see at a 20 × magnification but could be visualized at a 40 × magnification in more than 10% of tumor cells (score 2), and staining that could be visualized at 10 × magnification in more than 10% of tumor cells (score 3). Ubiquitin C (UBC) served as the positive control. Samples were considered adequate for analysis when the UBC mRNA signals were easily visible under a 10 × magnification objective lens (Fig. 2).

Immunohistochemical staining was performed using an automatic immunostainer, according to the manufacturer's instructions. The primary antibody was anti-total MET (SP44; rabbit monoclonal; prediluted, Ventana Medical Systems, Tucson, AZ). Briefly, 4-μm thick whole-tissue sections were transferred to poly-L-lysine-coated adhesive slides and dried for 30 min at 74 °C. After standard heat epitope retrieval in ethylenediaminetetraacetic acid (EDTA, pH 8.0) for 1 h, samples were incubated with antibodies against estrogen receptor (ER; 1:50 dilution, DAKO, Santa Clara, CA), progesterone receptor (PR; 1:200 dilution, DAKO, Santa Clara, CA), human epidermal growth factor receptor 2 (HER2; 1:500 dilution, Ventana Medical Systems, Tucson, AZ), and Ki-67 (clone SP6; 1:50 dilution, DAKO, Santa Clara, CA) using an autostainer. Sections were subsequently incubated with the appropriate reagents from the ultraView Universal DAB Kit (Ventana Medical Systems, Inc.) and counterstained with Harris hematoxylin.

A semiquantitative approach was used to generate a score for each tissue core as follows: no membrane staining or membrane staining in $<$ 10% of tumor cells (score 0), faint/barely perceptible partial membrane staining in $<$ 10% of tumor cells (score 1), weak-to-moderate staining of the entire membrane in $>$ 10% of tumor cells (score 2), and strong staining of the entire membrane in $>$ 10% of tumor cells (score 3). Scores of 0 and 1 were considered negative for MET overexpression, and scores of 2 and 3 were considered positive for MET overexpression (Fig. 1).

A cut-off value of at least 10% positively stained nuclei was used to define ER and PR positivity. Membrane staining for HER2 was classified as follows: membranous staining in 0–10% of cells (score 0), faint incomplete staining in at least 10% of cells (score 1+), weak to moderate complete staining in at least 10% of cells (2+), and strong complete staining in at least 10% of cells (3+). HER2 overexpression

Table 1. Patient demographics and characteristics

Characteristics		No. of patients (%)
Mean age, years (range)	49 (25–79)	
Histologic grade	1	85 (24.6)
	2	142 (41.0)
	3	119 (34.4)
T stage	T1	203 (54.7)
	T2	150 (40.4)
	T3	18 (4.9)
N stage	N0	231 (62.3)
	N1	86 (23.2)
	N2	23 (6.2)
	N3	31 (8.4)
AJCC stage	I	151 (40.7)
	II	163 (43.9)
	III	57 (15.4)
HR status	Negative	131 (35.9)
	Positive	234 (64.1)
HER2	Negative	303 (82.8)
	Positive	63 (17.2)
Intrinsic type	Luminal A	215 (58.9)
	Luminal B	19 (5.2)
	HER2 overexpression	44 (12.1)
	Triple Negative	87 (23.8)
Hormone therapy	No	62 (25.8)
	Yes	178 (74.2)
Adjuvant chemotherapy	No	50 (20.8)
	Yes	190 (79.2)

Abbreviations: AJCC, American Joint Committee on Cancer; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

was defined as a score of 3+. Cell staining for Ki-67 and p53 was expressed as a percentage. The Ki-67 labeling index was graded as low if the number of positive cells was $< 10\%$ and high if the number of positive cells was $> 10\%$. P53 was classified as positive when $> 10\%$ of cells were positively stained with a strong intensity.

Statistical analysis was performed using the SPSS software, version 15.0. Pearson's $\chi 2$ test was used to examine the correlation between variables. Survival analyses were performed using a Kaplan-Meier curve and the log-rank test. The Cox proportional hazard model was used for the survival analysis. All p values < 0.05 were considered statistically significant.

Results

The clinical characteristics of the 371 patients included in the present study are summarized in Table 1. Thirty-four patients experienced relapse, and 11 patients died of breast cancer-related causes. The median follow-up period was 48 months (range 7–74). The median recurrence-free survival (RFS) time was 45 months.

Among the 353 cases for which IHC information was available, the frequency of MET IHC positive cases was 13.0% (46/353); 11.9% (42/353) was the frequency of cases with score 1 and 1.1% (4/353) was the frequency of cases with score 2. There were no score 3 cases. However, there were score 3 areas in the ductal carcinoma in situ (DCIS) portion accompanied by invasive ductal carcinoma (IDC). IHC scores 1 and 2 were categorized as high MET protein expression.

Among the 364 cases for which MET ISH information was available, the frequency of ISH positive cases was 76.1% (277/364). The frequency breakdown by ISH score was as follows: 64.8% (236/364) score 1, 4.9% (18/364) score 2, 6.3% (23/364) score 3, and 1.1% (4/364) score 4. ISH scores 2–4 (45 cases, 12.4%) were categorized as high *MET* mRNA expression.

MET IHC results showed that high MET expression was significantly associated with high histologic grade, negative ER, negative PR, HER2 overexpression, triple negative tumor, and CK5 and EGFR expression. MET RNAscope in situ hybridization showed that high MET mRNA expression was significantly associated with high histologic grade, negative ER, negative PR, HER2 overexpression, triple negative tumor, p53 overexpression, and EGFR expression. MET mRNA and protein expression were found to be

Table 2. Clinicopathologic correlation of MET immunohistochemistry and mRNA in situ hybridization results in invasive breast cancer

		MET Protein (IHC)					MET RNA (ISH)				
		Low		High			Low		High		
		N	%	N	%	*p* value	N	%	N	%	*p* value
	Total	307	87	46	13		319	87.6	45	12.4	
Age (years)	< 50	183	59.6	28	60.9	0.871	185	58	30	66.7	0.268
	> 50	124	40.4	18	39.1		134	42	15	33.3	
Histologic grade	1	201	70.3	14	32.6	< 0.001	212	71.1	13	31	< 0.001
	2 or 3	85	29.7	29	67.4		86	28.9	29	69	
N stage	N0	187	67.5	32	69.6	0.782	192	66.7	33	73.3	0.374
	N1	90	32.5	14	30.4		96	33.3	12	26.7	
AJCC	I	210	68.4	38	82.6	0.049	220	69	36	80	0.129
	II-IV	97	31.6	8	17.4		99	31	9	20	
ER	Negative	119	38.9	29	63	0.002	120	37.9	33	73.3	< 0.001
	Positive	187	61.1	17	37		197	62.1	12	26.7	
PR	Negative	132	43.1	29	63	0.012	135	42.6	31	68.9	0.001
	Positive	174	56.9	17	37		182	57.4	14	31.1	
HER2 overexpression	Absent	258	84.3	31	67.4	0.005	268	84.5	31	68.9	0.01
	Present	48	15.7	15	32.6		49	15.5	14	31.1	
Intrinsic type	Luminal A	193	63.3	15	32.6	0.001	203	64.2	11	24.4	< 0.001
	Luminal B	15	4.9	4	8.7		16	5.1	3	6.7	
	HER2 overexpression	33	10.8	11	23.9		33	10.4	11	24.4	
	Triple Negative	64	21	16	34.8		64	20.3	20	44.4	
Triple Negative vs. non-TN	Triple Negative	64	21	16	34.8	0.038	64	20.3	20	44.4	< 0.001
	Non-TN	241	79	30	65.2		252	79.7	25	55.6	
p53	Negative	220	74.8	31	67.4	0.286	234	77	23	52.3	< 0.001
	Positive	74	25.2	15	32.6		70	23	21	47.7	
CK5	Negative	140	50.9	15	34.1	0.038	142	49.7	17	41.5	0.327
	Positive	135	49.1	29	65.9		144	50.3	24	58.5	
EGFR	Negative	254	88.5	32	72.7	0.004	266	89	30	71.4	0.002
	Positive	33	11.5	12	27.3		33	11	12	28.6	

Abbreviations: IHC, immunohistochemistry; ISH, in situ hybridization; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TN, triple negative; CK, cytokeratin; EGFR, epidermal growth factor receptor.

significantly associated with aggressive histologic features and the hormone receptor-negative phenotype in breast cancers (Table 2).

In the 353 invasive breast cancers studied, there was a positive correlation between MET mRNA and protein expression ($r = 0.583$, $p < 0.001$; Table 3). All four cases with an RNA ISH score of 4 showed MET protein expression. Among the 23 cases with an RNA ISH score of 3, 14 cases (75%) showed an IHC score of 2, and two cases (9%) showed an IHC score of 3.

Kaplan-Meier analyses of MET IHC and ISH data showed no significant correlation with overall survival (OS) or RFS. Subgroup analyses of lymph node metastasis, hormone receptor expression, hormone therapy, and adjuvant chemotherapy showed no significant association of OS or RFS with MET protein or mRNA expression. In the multivariate survival analysis, MET positivity was not an independent prognostic factor for OS or RFS.

Discussion

The main purpose of this retrospective study was to assess the possible correlation of MET mRNA expression (RNAscope in situ hybridization) and MET protein expression (IHC) in invasive breast cancers; a strong positive correlation was identified. Previously, it was shown that the mRNA expression of HER2 [17] and MET [18], as evaluated by RNA ISH, was well-correlated with protein overexpression and gene amplification, which were evaluated by IHC and FISH, respectively.

High levels of MET expression have been found in a variety of epithelial tumors. Several cancer cell lines exhibiting MET gene amplification, such those from non-small cell lung carcinomas (NSCLCs) and in gastric carcinomas, are dependent on MET for growth and survival, and MET

Table 3. Correlation of MET mRNA scores (assessed by RNA in situ hybridization) with MET protein scores (assessed by immunohistochemistry)

MET mRNA scores (ISH)	MET protein scores (IHC)			
	0 (n = 307)	1 (n = 42)	2 (n = 4)	*p* value
0 (n = 76)	76 (100%)	0 (0%)	0 (0%)	< 0.001
1 (n = 232)	216 (93%)	16 (7%)	0 (0%)	
2 (n = 18)	8 (44%)	9 (50%)	1 (6%)	
3 (n = 23)	7 (30%)	14 (61%)	2 (9%)	
4 (n = 4)	0 (0%)	3 (75%)	1 (25%)	

Abbreviations: IHC, immunohistochemistry; ISH, in situ hybridization.

inhibition in these cell lines results in decreased cell proliferation and death [19, 20]. The most frequent cause of constitutive MET activation in human cancers is protein overexpression resulting from transcriptional upregulation in the absence of gene aberrations [21]. It is fairly well known that amplification of MET is not a common event in breast cancer, relative to other cancer subtypes (renal, gastric, and lung carcinomas). In breast cancer, it seems that overexpression of MET is not typically caused by the increased gene copy number of MET/polysomy7 [21].

The simplest molecular mechanism of MET activation in tumor cells, which involves HGF-dependent MET activation, also occurs in normal cells. In some cases, tumor cells express both HGF and its receptor, enabling an autocrine loop in which secreted HGF binds to MET, causing constitutive activation of MET and its downstream signaling pathways and thus enhancing tumor growth and invasive behavior. Such HGF-MET autocrine loops have been detected in gliomas, osteosarcomas, and mammary, prostate, breast, lung, and other carcinomas; they are often associated with malignant progression of tumors and correlate with poor prognosis [21].

Among the subtypes of IDC, triple negative breast cancer is more associated with MET expression [10, 23]. When expressed in the mammary gland, MET can cause basal-like breast carcinomas [24]. MET was associated with poor OS in lymph node-negative breast cancer and with poor RFS in hormone receptor-positive and triple negative breast cancers, but it was not associated with prognosis in HER2-positive breast cancer [3]. Low protein expression of MET in ER-positive and HER2-positive breast cancer was reported [11]. The MET receptor is also associated with trastuzumab resistance of HER2-overexpressing breast cancer cells [7].

MET overexpression has been reported in 14–53.6% of patients with breast cancer [10, 25, 26]. In the current study, no statistically significant relationship was found between MET and breast cancer survival. Interestingly, in one meta-analysis of MET expression in breast cancer, MET overexpression was correlated with poor RFS and OS in western patients but not in Asian patients [3].

The present study confirmed that MET protein expression (determined through IHC) correlates with MET mRNA expression (determined through ISH) in invasive breast cancers.

Ethics approval and consent to participate

This study was approved by IRB of the Kangbuk Samsung Hospital (KBC14077) and written informed consent was waived.

Authors' contributions

SID: writing, data analysis, medical record review; HCS: medical record review; HSK: funding, data analysis, writing.

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Conflict of Interest

The authors declare no competing interests.

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