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Original Article

Clinical significance of c-Met and phospho-c-Met (Tyr1234/1235) in ovarian cancer

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ABSTRACT

Objective: c-Met is expressed in human ovarian cancer tissues, and its phosphorylation activates signaling cascades that might affect the behavior of cancer cells. In this study, we evaluated the association of c-Met and phosphorylated c-Met (phospho-c-Met) expressions with the clinical outcomes of ovarian cancer patients.

Materials and methods: Archived tissue from surgical specimens of 269 ovarian cancer patients who underwent a debulking operation in MacKay Memorial Hospital between 2004 and 2012 were collected. Tissue microarrays were stained with anti-Met and anti-phospho-Met (Tyr1234/1235) monoclonal antibodies. Immunostaining intensity was scored on a scale of 0–3+. High expression was defined as more than 50% of moderate and intense staining. Patients' clinical data were reviewed until April 2017 for analysis.

Results: The proportion of high c-Met expression was significantly higher in patients with cancer in early stages (Federation of Gynecology and Obstetrics stages I and II) and low histologic grades (grades 1 and 2) (79.70%, $p = 0.0008$ and 80.15%, $p \leq 0.0001$, respectively). However, no association was found between phospho-c-Met and FIGO stage or the histologic grade. Ovarian clear cell carcinoma and mucinous carcinoma had much higher c-Met expression (95.16% and 87.10%, $p \leq 0.0001$ and $p = 0.0292$, respectively). Although the overall survival did not differ significantly, low expressions of c-Met and phospho-c-Met were obviously associated with poor progression-free survival respectively ($p = 0.0034$, HR: 0.5264, 95% CI: 0.3326–0.8330 and $p = 0.0136$, HR: 0.5626, 95% CI: 0.3709–0.8535).

Conclusion: Low c-Met expression was associated with poor clinical outcomes.

Introduction

Ovarian cancer is a life-threatening gynecologic tumor and is often diagnosed at an advanced stage. Despite initial response to treatment, 70% of patients with ovarian cancer ultimately develop recurrence. Unfortunately, there has been no significant improvement in the outcome of these patients over the past two decades. The aggressive metastatic behavior of ovarian cancer has driven the pursuit of target therapy; Met inhibitors are one of these therapeutic agents. c-Met is expressed in approximately 70% of human ovarian cancer tissues [1–3]. The *MET* gene is located at chromosome 7q31.2, and c-Met is a transmembrane receptor. The binding of its ligand, the hepatocyte growth factor (HGF), phosphorylates c-Met, which activates downstream signaling pathways [4] that induce cell proliferation, motility, and angiogenesis [5]. c-Met might not only play crucial physiologic roles in embryogenesis, organ development, and tissue regeneration, but also contribute to the aggressiveness of cancer cells.

However, the clinical implication of c-Met and phospho-c-Met expressions remains controversial. Meta-analyses of esophageal, colorectal, and breast cancers have shown a correlation of high c-Met expression with poor clinical outcomes [6–8]. Clinical studies of locally advanced nasopharyngeal carcinoma and advanced gastric cancer have also reported an association of poor prognosis with high c-Met expression [9,10]. A meta-analysis of cervical cancer indicated that c-Met can be a potential diagnostic and

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prognostic indicator because high c-Met expression correlated well with short disease-free survival, high lymph node involvement, and lymphovascular space invasion [11]. Similarly, a study of 60 cases of endometrial adenocarcinoma found that high c-Met expression was significantly correlated with a higher histological grade [12]. By contrast, a study on non–small-cell lung cancer found no significant association between c-Met expression and clinical prognosis [13]. Another study found that c-Met mRNA expression in hepatocellular carcinoma was correlated with early-stage disease and favorable clinicopathological characteristics, although there was no influence on survival [14]. The prognostic power of c-Met expression in ovarian cancer is debatable. Studies on late-stage ovarian cancer patients [15] and ovarian clear cell carcinoma patients [16] have demonstrated an association of high c-Met expression with poor prognosis. By contrast, Battista et al. showed no correlation between c-Met expression and clinical outcomes [17].

To further understand the role of c-Met and phospho-c-Met in ovarian cancer, we investigated the correlation between c-Met and phospho-c-Met expressions and the clinical outcomes of patients with ovarian cancer.

Materials and methods

Patients and tissue microarrays

Archived tissue blocks from 269 patients who had undergone debulking surgery at MacKay Memorial Hospital between 2004 and 2012 were enrolled in this study under the approval of IRB (14MMHIS286). Patients' charts were reviewed until April 2017, and pathological reports were reviewed to document the histologic grade and subtype and tumor stage. Histologic grade was not documented in 48 patients because it was not required for the staging system in earlier years or for certain histologic subtype according to the International Federation of Gynecology and Obstetrics (FIGO) system. Surgery was defined as *optimal debulking* if residual disease was $\leq$1 cm and as *suboptimal debulking* if residual disease was >1 cm. Mortality from ovarian cancer and other causes were documented. Three 0.4-mm cores were punched from a certain section of each tissue block, which was determined by one gynecologic pathologist. The samples were stained with hematoxylin–eosin to confirm the presence of tumor.

Immunohistochemistry

Slides of tissue arrays were deparaffinized and rehydrated. After antigen retrieval, blocking was performed using a protein blocker (Dako Cytomation, Carpinteria, CA), followed by overnight incubation with anti-Met Rabbit monoclonal antibody (1:300 dilution; clone D1C2; Cell Signaling, Beverly, MA, USA) and anti-phospho-Met (Tyr1234/1235) Rabbit monoclonal antibody (1:160 dilution; clone D26; Cell Signaling) at 4 °C and then washed. Secondary antibody amplification and visualization were achieved by ChemMate DAKO EnVision Detection Kit, Peroxidase/DAB, Rabbit/Mouse (Dako Cytomation, Carpinteria, CA). The tissue sections were dehydrated and counterstained with Mayer's hematoxylin. The slides were scanned and saved using the TissueFAXS system. Immunostaining intensity was scored on a scale from 0 (no staining) to 3+ (intense staining). As in HercepTest, the immunostaining intensity was defined as: 0, no discernible staining or background type staining; 1 + definite cytoplasmic staining and/or equivocal discontinuous membrane staining; 2 + unequivocal membrane staining with mild to moderate intensity; 3+, strong and complete membrane staining. The extent of immunoreactivity was documented as the percentage of epithelial tumor cells that stained positive. *High expression* was defined as >50% of tumor cells with a staining intensity score of 2–3+ (Fig. 1) as in the MetMab trial [18]. Two trained reviewers scored all these slides independently. A gynecologic pathologist resolved the discrepancies between them.

Statistical analysis

Statistical analyses were performed using SPSS (version 24.0, IBM, Armonk, New York) and GraphPad Prism (version 7.00 for Mac, GraphPad Software, La Jolla California USA). Correlations between clinicopathological factors and the expression of c-Met and phospho-c-Met were evaluated using the χ^2 test or Fisher's exact test. Progression-free survival (PFS) and overall survival (OS) were measured using the Kaplan–Meier method, and comparisons were computed using the log-rank test. Univariate and multivariate Cox-regression analysis for PFS and OS were performed. PFS was defined as the time between the date of pathological proof and the date of first progression after surgery. OS was defined as the time between the date of pathological proof and the date of last follow-up or death. All statistical tests were two-sided.

Results

A total of 269 patients were enrolled. Their mean age was 51.43 (±10.98) years, and the mean follow-up duration was 62.8 months. During this study, 94 (34.94%) cases of recurrence and 91 (33.83%)

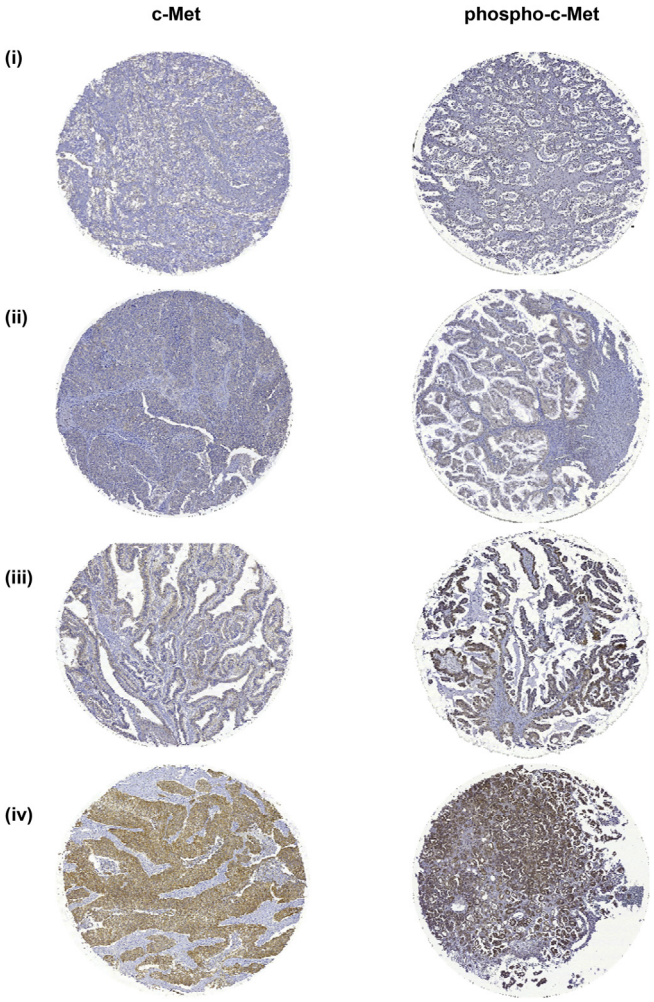

Fig. 1. Immunohistochemistry staining of tissue microarrays. Representative examples of staining against c-Met and phospho-c-Met of (i) no staining; (ii) weak staining; (iii) moderate staining; and (iv) strong staining.

cases of mortality occurred; four of the 91 patients died due to other cancers or diseases. The characteristics of patients are presented in Table 1.

The proportion of patients in early stages (FIGO stages I and II) and late stages (FIGO stages III and IV) was similar (49.44% and 46.47%, respectively). Serous carcinoma (34.94%) and clear cell carcinoma (23.05%) patients comprised over half of the cohort, and 5.95% had other histologic subtypes, including malignant mixed Müllerian tumor (n = 4), germ cell carcinoma (n = 3), transitional cell carcinoma (n = 3), poorly differentiated carcinoma (n = 2), and one case each of carcinosarcoma, undifferentiated carcinoma, and high-grade carcinoma. Patients were stratified into two groups according to the FIGO histologic grade: 59.28% had grade 1–2 and 40.72% had grade 3; 48 cases were not assigned a histologic grade. Most patients (90.33%) underwent optimal debulking surgery, and only 2.97% received neoadjuvant chemotherapy; 76.03% received taxane and platinum chemotherapy as the first-line chemotherapy.

The correlation of c-Met with clinicopathological factors is presented in Table 2. In this cohort, 189 patients (70.26%) had high c-Met expression. A higher proportion of early-stage patients (79.70%) had high c-Met expression than that of late-stage patients (60%; p = 0.0005). Moreover, high c-Met expression was also associated with early-histologic grade (grades 1 and 2) patients (80.15%, p ≤ 0.0001). A higher proportion of patients with serous carcinoma and other histologic subtypes had low c-Met expression (53.19%, p ≤ 0.0001 and 56.25%, p = 0.0168, respectively). By contrast, a significantly higher proportion of patients with clear cell carcinoma and mucinous carcinoma had high c-Met expression (95.16%, p ≤ 0.0001 and 87.10%, p = 0.0292, respectively).

Ninety-nine patients had high phospho-c-Met expression (36.80%) in our cohort. The correlation of phospho-c-Met with clinicopathological factors is presented in Table 3. There were no

Table 1
Patient characteristics.

Patient characteristics (*n* = 269)		
Mean age, years (±SD)	51.43	(±10.98)
Age (years) *n* (%)		
≤50	126	(46.84)
>50	143	(53.16)
FIGO stage, *n* (%)		
Early stage (I, II)	133	(49.44)
Late stage (III, IV)	125	(46.47)
Recurrent	11	(4.09)
Histologic grade, *n* (%)[a]		
G1 + G2	131	(59.28)
G3	90	(40.72)
Histologic subtype, *n* (%)		
Serous carcinoma	94	(34.94)
Clear cell carcinoma	62	(23.05)
Endometrioid carcinoma	32	(11.90)
Mucinous carcinoma	31	(11.52)
Mixed type	34	(12.64)
Others	16	(5.95)
Residual tumor (cm), *n* (%)		
≤1	243	(90.33)
>1	26	(9.67)
Chemotherapy, *n* (%)		
Taxane and platinum	203	(76.03)
Platinum and other	27	(10.11)
Other/unknown	8	(3.00)
None	29	(10.86)
Chemotherapy type, *n* (%)		
Primary	232	(86.25)
Neoadjuvant	8	(2.97)
None	29	(10.78)
Median CA125, U/mL	5606	

[a] *n* = 221, the histologic grade was given according to FIGO classification in year of diagnosis. SD, standard deviation; FIGO, International Federation of Gynecology and Obstetrics.

Table 2
Correlation of c-Met with regard to clinicopathological factors.

	c-Met				p-value
	High expression		Low expression		
	N	%	N	%	
Total number of cases	189	70.26	80	29.74	
Age					
≤50 years	95	75.40	31	24.60	0.0836
>50 years	94	65.73	49	34.27	
FIGO stage					
Early stage (I, II)	106	79.70	27	20.30	*0.0005*
Late stage (III, IV)	75	60.00	50	40.00	
Histologic grade					
G1 + G2	105	80.15	26	19.85	*<0.0001*
G3	49	54.44	41	45.56	
Histologic subtype					
Serous carcinoma	44	46.81	50	53.19	*<0.0001*
Clear cell carcinoma	59	95.16	3	4.84	*<0.0001*
Endometrioid carcinoma	25	78.13	7	21.88	0.2998
Mucinous carcinoma	27	87.10	4	12.90	*0.0292*
Mixed type	27	79.41	7	20.59	0.2117
Others[a]	7	43.75	9	56.25	*0.0168*

There were 80% of early stage and histologic G1+G2 patients with high c-Met expression (79.70% and 80.15%, p = 0.0005 and p < 0.0001, respectively). A significantly higher proportion of patients with ovarian serous carcinoma and others histologic subtypes had low c-Met expression (53.19% and 56.25%; p ≤ 0.0001 and p = 0.0168, respectively). On the other hand, a significant higher proportion of patients with ovarian clear cell carcinoma and ovarian mucinous carcinoma had high c-Met expression (95.16% and 87.10%; p ≤ 0.0001 and p = 0.0292, respectively).

[a] Others histologic subtypes included malignant mixed Müllerian tumor (n = 4), germ cell carcinoma (n = 3), transitional cell carcinoma (n = 3), poorly differentiated carcinoma (n = 2), and one case of carcinosarcoma, undifferentiated carcinoma, and high-grade carcinoma each; FIGO, International Federation of Gynecology and Obstetrics.

Table 3
Correlation of phospho-c-Met with regard to clinicopathological factors.

	phospho c-Met				p-value
	High expression		Low expression		
	N	%	N	%	
Total number of cases	99	36.80	170	63.20	
Age					
≤50 years	51	40.48	75	59.52	0.2410
>50 years	48	33.57	95	66.43	
FIGO stage					
Early stage (I, II)	53	39.85	80	60.15	0.2983
Late stage (III, IV)	42	33.60	83	66.40	
Histologic grade					
G1 + G2	48	36.64	83	63.36	0.5022
G3	37	41.11	53	58.89	
Histologic subtype					
Serous carcinoma	22	23.40	72	76.60	*0.0008*
Clear cell carcinoma	19	30.65	43	69.35	0.2518
Endometrioid carcinoma	11	34.38	21	65.63	0.7616
Mucinous carcinoma	15	48.39	16	51.61	0.1551
Mixed type	21	61.76	13	38.24	*0.0012*
Others[a]	11	68.75	5	31.25	*0.0063*

A significantly higher proportion of patients with ovarian serous carcinoma had low phospho-c-Met expression (76.60%, p = 0.0008). By contrast, a significant higher proportion of patients with mixed type and others histologic subtypes had high phospho-c-Met expression (61.76% and 68.75%; p = 0.0012 and 0.0063, respectively).

[a] Others histologic subtypes included malignant mixed Müllerian tumor (n = 4), germ cell carcinoma (n = 3), transitional cell carcinoma (n = 3), poorly differentiated carcinoma (n = 2), and one case of carcinosarcoma, undifferentiated carcinoma, and high-grade carcinoma each; FIGO, International Federation of Gynecology and Obstetrics.

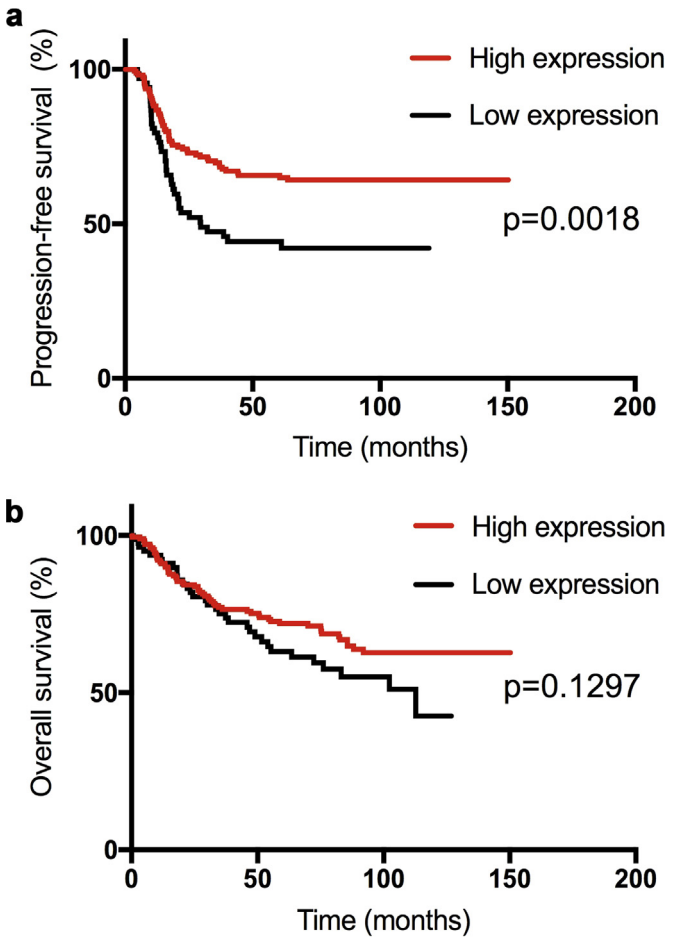

Fig. 2. Kaplan–Meier survival curves of patients with regard to c-Met expression. (a) Progression-free survival of low c-Met expression was significantly worse (p = 0.0018, HR: 0.5263, 95% CI: 0.3326–0.8330). (b) Overall survival did not reach significant difference between these two groups (p = 0.1297, HR: 0.7201, 95% CI: 0.4580–1.1320).

significant differences in the expression of phospho-c-Met among different groups of FIGO stages and histologic grades. A significantly higher proportion of serous carcinoma patients had low phospho-c-Met expression (76.60%, p = 0.0008). By contrast, a significantly higher proportion of patients with the mixed type and other histologic subtypes had high phospho-c-Met expression (61.76%, p = 0.0012 and 68.75%, p = 0.0063, respectively).

PFS was significantly poorer in patients with low c-Met expression [p = 0.0018, HR: 0.5263, 95% CI: 0.3326–0.8330; Fig. 2 (a)]. However, OS showed no difference [p = 0.1297, HR: 0.7201, 95% CI: 0.4580–1.1320, Fig. 2 (b)]. Similarly, PFS was significantly poorer in patients with low phospho-c-Met expression [p = 0.0136, HR: 0.5626, 95% CI: 0.3709–0.8535; Fig. 3 (a)]; however, OS showed no difference [p = 0.4808, HR: 0.8547, 95% CI: 0.5578–1.3100; Fig. 3 (b)].

Univariate Cox-regression analysis showed c-Met and phospho-c-Met were associated with poorer PFS [p = 0.0022, HR: 0.5245, 95% CI: 0.3470–0.7928; p = 0.0150, HR: 0.5623, 95% CI: 0.3536–0.8941, Table 4(A)] but not OS. Moreover, c-Met was associated with PFS in multivariate Cox-regression analysis [p = 0.0332, HR: 0.6292, 95% CI: 0.4109–0.9637, Table 4(A)].

Discussion

In the present study, we observed a significantly lower PFS associated with low expressions of c-Met and phospho-c-Met despite no difference in OS. c-Met modulates cell normal development and carcinogenesis. The binding of HGF to c-Met phosphorylates two tyrosine residues and activates downstream signaling pathway such as PI3K-Akt, RAS-MAP kinase, STAT3, and nuclear factor-kB complex [4]. High expression of c-Met was found in various cancers [19], including ovarian cancer [20]. Studies have shown that 30%–70% of ovarian cancer patients had high expression of c-Met [1,15,21,22]. In this study of 269 ovarian cancer patients, 70.26% of patients had high expression of c-Met.

The association between c-Met expression and prognosis remained controversial. Sawada et al. analyzed 138 late-stage (stages III and IV) ovarian cancer patients and concluded that patients with high c-Met expression had a significantly poorer prognosis, with lower median OS (32 vs. 17 months, p = 0.0015) but no difference in PFS [15]. Similarly, Yamamoto et al. demonstrated that high c-Met expression had a negative influence on OS (p = 0.0176) in 90 clear cell adenocarcinoma patients [16].

On the other hand, Battista et al. studied 106 ovarian cancer patients and exhibited no significant association between c-Met expression with PFS and disease-specific survival [17]. By contrast, Goode et al. showed that phospho-c-Met was associated with reduced mortality (p = 0.01) and found higher expression of phospho-c-Met in early-stage patients [23].

The prognostic role of c-Met and phospho-c-Met in ovarian cancer is uncertain as the underlying mechanisms remain unknown. In the present study, we sought to investigate the clinical

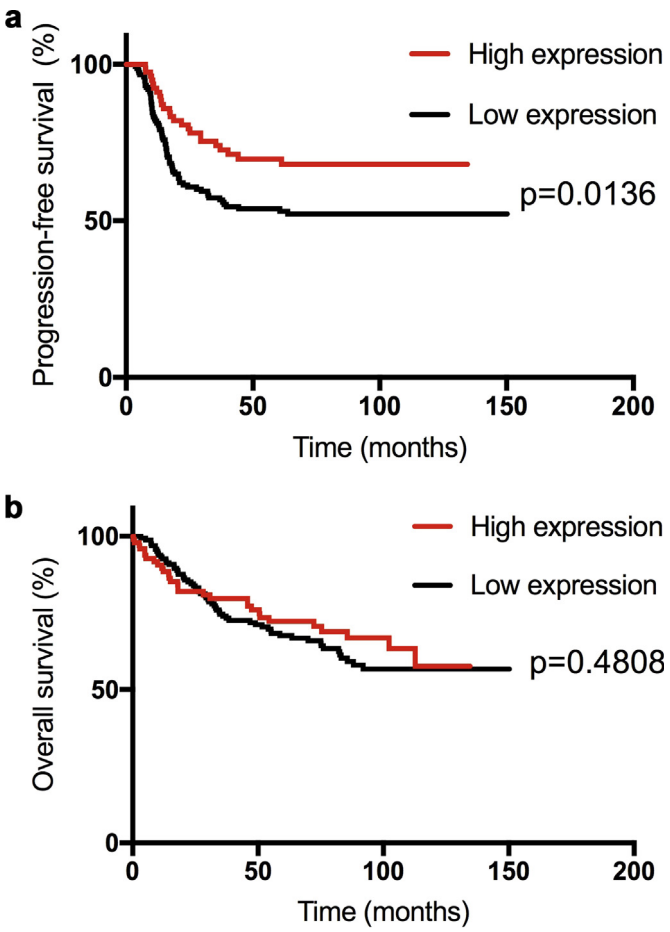

Fig. 3. Kaplan–Meier survival curves of patients with regard to phospho-c-Met expression. (a) Progression-free survival of low phospho-c-Met expression was significantly worst (p = 0.0136, HR: 0.5626, 95% CI: 0.3709–0.8535). (b) Overall survival did not reach significant difference between these two groups (p = 0.4808, HR: 0.8547, 95% CI: 0.5578–1.3100).

Table 4
Univariate and multivariate Cox-regression analysis for progression-free and overall survival.

Parameter	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
A. Progression-free survival				
Age (>50y/o)	1.1310 (0.7545–1.6954)	0.5510		
CA125	1.000 (1.0000–1.0000)	0.9326		
Tumor stage				
Late	8.3785 (5.0210–13.9813)	*<0.0001*	6.8865 (3.9399–12.0369)	*<0.0001*
Recurrent	4.8647 (1.8143–13.0436)	*0.0017*	4.7276 (1.7281–12.9335)	*0.0025*
Residual tumor burden	4.5662 (2.5666–8.1234)	*<0.0001*	1.9763 (1.0546–3.7035)	*0.0335*
Chemotherapy				
Neoadjuvant	5.8025 (1.7867–18.8441)	*0.0034*	2.4787 (0.7037–8.7307)	0.1576
No adjuvant	0.2600 (0.0822–0.8220)	*0.0218*	0.9025 (0.2629–3.0989)	0.8706
c-Met	0.5245 (0.3470–0.7928)	*0.0022*	0.6292 (0.4109–0.9637)	*0.0332*
phospho-c-Met	0.5623 (0.3536–0.8941)	*0.0150*	0.6521 (0.4055–1.048)	0.0778
B. Overall survival				
Age (>50y/o)	1.4502 (0.9546–2.2031)	0.0815		
CA125	1.0000 (1.0000–1.0000)	0.4031		
Tumor stage				
Late	7.8741 (4.4984–13.7828)	*<0.0001*	8.4635 (4.4383–16.1393)	*<0.0001*
Recurrent	3.0810 (0.8914–10.6485)	0.0754	3.6844 (1.0265–13.2242)	*0.0455*
Residual tumor burden	3.3625 (1.9506–5.7964)	*<0.0001*	1.5121 (0.8467–2.7003)	0.1622
Chemotherapy				
Neoadjuvant	4.2081 (1.8107–9.7795)	*0.0008*	1.8365 (0.7606–4.4343)	0.1765
No adjuvant	0.5467 (0.2215–1.3497)	0.1903	2.1154 (0.7577–5.9058)	0.1526
c-Met	0.7194 (0.4689–1.1037)	0.1315		
phospho-c-Met	0.8546 (0.5520–1.3233)	0.4813		

c-Met was associated with PFS in univariate and multivariate Cox-regression analysis. HR, hazard ratio; CI, confidence interval.

significance of c-Met and phospho-c-Met in ovarian cancer patients. We stratified the patients according to histologic grade and FIGO stage. Our study showed a significantly higher proportion of early histologic grade (grades 1 and 2) and early stage (FIGO stages I and II) patients presented with high c-Met expression. In other words, low c-Met expression was associated with late disease status. Furthermore, phospho-c-Met expression was found to have the same trend, although it did not reach significance. When analyzing by different histologic subtypes, a significantly high proportion of patients with clear cell carcinoma or mucinous carcinoma had high c-Met expression. Our data was consistent with a previous study that showed high c-Met expression in clear cell carcinoma [16].

Finally, low c-Met and low phospho-c-Met expressions were correlated with poor PFS respectively. This finding is consistent with our data that showed low c-Met and phospho-c-Met expressions to be associated with late disease status. Moreover, low c-Met and phospho-c-Met expressions were also associated with lower OS, although these did not reach significant difference. Furthermore, multivariate Cox-regression analysis of c-Met expression was associated with PFS. These data were inconsistent with those of Sawada et al. [15], which showed poorer prognosis in patients with high c-Met expression. One possibility could be the difference in study populations. Their study consisted of 82.6% serous papillary adenocarcinoma patients, while our study comprised only 34.94% of serous carcinoma patients. Besides, this study included a high proportion of clear cell carcinoma patients (23.05%). High c-Met expression was shown to be associated with type I rather than type II ovarian cancer as c-Met is believed to be involved in the carcinogenesis of type I ovarian cancer [17]. Our cohort consisted of high proportion of type II ovarian cancer and only 82 (30.48%) cases of high-grade serous ovarian cancer. In addition, Sawada et al. study [15] included only late-stage patients; whereas we analyzed the prognostic impact of c-Met in the full spectrum of ovarian cancer patients, with 133 early-stage patients, 125 late-stage patients, and 11 recurrent disease patients. Another possibility could be the inconsistent categorization of c-Met expression among studies. We evaluated the immunohistochemistry results quantitatively and qualitatively. However, several combinations could result in different interpretations between researchers. There is no consensus on cut-off values of high and low c-Met and phospho-c-Met expressions. Moreover, different methods in evaluating and categorizing immunohistochemistry results might, in turn, alter the result.

In conclusion, this study helps to understand the clinical significance of c-Met and phospho-c-Met on ovarian cancer. Our data indicated that low expressions of c-Met and phospho-c-Met correlated with poor prognosis. Further investigations using genomic or proteomic approach might provide a clear insight.

Conflict of interest

All authors have nothing to disclose.

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