Protein overexpression of c-MET has a significant impact on survival in patients with uterine cervical adenocarcinoma

Shin Hee Seo[2], Wook Youn Kim[1], Seung-Hyuk Shim[2], Jin Hee Park[3], Hyung Kyu Park[3], Sun Joo Lee[2]
[1]Department of Pathology, Konkuk University School of Medicine, Seoul, Korea
[2]Department of Obstetrics and Gynecology, Konkuk University School of Medicine, Seoul, Korea
[3]Department of Pathology, Konkuk University Medical center, Seoul, Korea

OBJECTIVE

We investigated the association between MET protein expression using immunohistochemistry(IHC) and gene copy number(GCN) as evaluated using silver *in situhybridization(SISH*) in Korean patients with uterine cervical cancer. We also would like to determine whether MET status using these two methods was associated with prognosis to provide a new treatment method for Korean patients with cervical cancer.

MATERIAL AND METHODS

We analyzed total 117 cases of uterine cervical cancer from Aug. 2005 to Aug. 2018. All patients underwent standard treatment and followed up at KonKuk University Hospital, South Korea.

More than ≥2+ in immunohistochemistry(IHC) was considered as positive results in MET expression. *MET GCN* were assessed by Silver *in-situ* hybridization(SISH) *and MET* gene status was divided into six different groups. High polysomy(HP) and gene amplification(GA) were considered as SISH positivity, and others indicate the opposite.

RESULTS

MET protein expression

The cancer cases assigned as having MET overexpression did not show significant differences in OS and PFS compared with the cancer cases that were not assigned as having overexpression (*P* = 0.958 and P = 0.799). However, the cancer cases assigned as having MET IHC 3+ showed significantly longer OS and PFS compared with the cancer cases that were assigned as having IHC 0/1+/2+ (*P* = 0.001 and P = 0.000).

MET GCN

The cancer cases assigned as having positive MET SISH did not show a significantly different OS and PFS compared with the cancer cases that were assigned as having negative MET SISH (P = 0.307 and P = 0.184; Figure). However, positive MET SISH cases showed worse tendencies of OS and PFS compared with negative MET SISH cases.

Table 1: Clinical characteristics of the patients with epithelial ovarian cancer

Parameter	Results (n=117)
Median age (range), y	49.0 (24-77)
Histotype, n (%)	
Squamous cell carcinoma	83 (70.9)
Adenocarcinoma	23 (19.7)
Endocervical adenocarcinoma, usual type	14
Mucinous adenocarcinoma, gastric type	4
Muconous adenocarcinoma, NOS	3
Serous adenocarcinoma	1
Clear cell adenocarcinoma	1
Adenosquamous cell carcinoma	7 (6.0)
others	4 (3.4)
FIGO stage, n (%)	
IB1 / IB2	89 (76.1) / 9 (7.7)
IIA1 / IIA2	8 (6.8) / 9 (7.7)
IVA* / IVB*	1 (0.9) / 1 (0.9)
Lymph node metastasis, n (%)	
NA[†]	6 (5.1)
No	77 (65.8)
Yes	34 (29.1)
Positive resection margin, n (%)	
No	104 (88.9)
Yes	13 (11.1)
Parametrial invasion, n (%)	
NA	7 (6.0)
No	96 (82.1)
Yes	14 (12.0)

Table 2: MET overexpression and copy number alteration in cervical cancer

Histotype	MET IHC				*MET* SISH				
	Negative	Positive			Negative	Positive			
	0 or 1+	2+	3+	*P*	DS, LT, or LP	HP	GA	NA	*P*
SCC	57 (68.7)	26 (31.3)	0	.007	70 (84.3)	3 (3.6)	0	10 (12.0)	.199
AC	6 (26.1)	12 (52.8)	5 (21.7)		17 (73.9)	3(13.0)	0	3 (13.0)	
ASCC	6 (85.7)	1 (14.3)	0		5 (71.4)	0	0	2 (28.6)	
Others	3 (75.0)	1 (25.0)	0		3 (75.0)	0	0	1 (25.0)	
Total (%)	72 (61.5)	40 (34.2)	5 (4.3)		95 (94.1)	6 (5.9)	0	16 (13.7)	

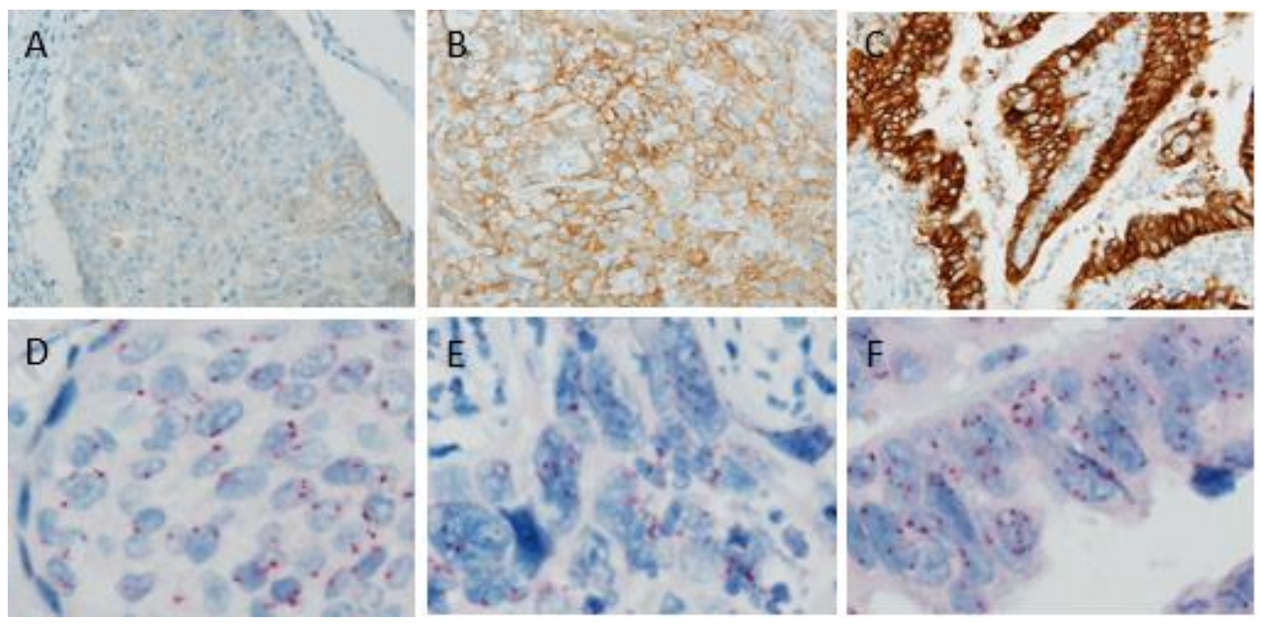
Prognostic significance of MET protein expression and clinicopathologic indicators for patients with cervical cancer

Significant factors associated with decreased OS were FIGO stage (P = .000), parametrial invasion (P = .001), LVSI (P = .011), and c-MET protein expression (IHC 3+) (P = .001) (Table 3). Multivariate analysis revealed that FIGO stage, LVSI, and IHC 3+ c-MET expression were independent variables associated with OS. FIGO stage (P = .002; hazard ratio [HR] = 0.03; 95% confidence interval [CI], 0.00-0.25), LVSI (P = .013; HR = 0.40; 95% CI, 0.20-0.83) and c-Met expression (P = .015; HR = 0.10; 95% CI, 0.02-0.64) were the most important predictors of the OS of patients (Table 3).

CONCLUSION

MET protein overexpression(IHC3+) was profoundly related to poorer PFS and OS, thus this indicates that overexpression in MET protein could be used as a biomarker of poor prognoses. However, *MET* GCN was not associated with any prognoses.

Elevated MET protein and worse prognoses show a significant correlation and suggest that IHC may be the preferred test to decide which cervical cancer patients needs anti-MET therapy. Anti-MET agents-applied therapy for cervical adenocarcinoma with overexpressed MET protein cancer may produce desirable results.



(A-C)Three images of cervical carcinomas express IHC score 1+(A,squamous cell carcinoma), 2+(squamous cell carcinoma), and 3+(C,usual type endocervical adenocarcinoma), individually.
(D-E)Three representative SISH images of disomy in squamous cell carcinoma(D), high polysomy in squamous cell carcinoma(E), and high polysomy in serous adenocarcinoma(F) are shown.

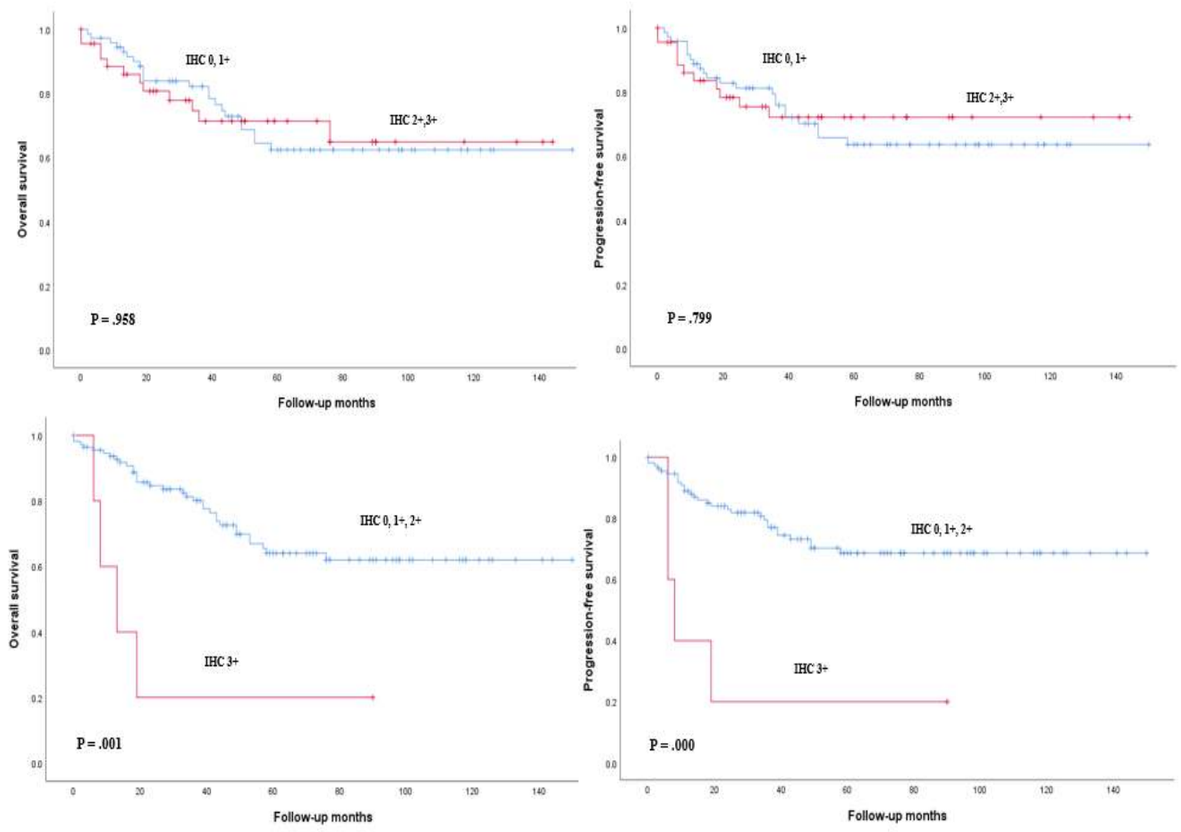


Table 3: Cox proportional analyses of the association between prognostic variable and overall survival in cervical cancer

	Univariate analysis	Multivariate analysis	
	P value	Hazard ratio [95% CI]	P value
FIGO stage (Ib /IIa / ≥IIb)	.000	0.03 [0.00-0.25]	.002
Histotypes	.743	NA	
Lymph node metastasis	.231	NA	
Parametrial invasion	.001	0.84 [0.26-2.75]	.777
Positive resection margin	.151	NA	
LVSI	.011	0.40 [0.20-0.83]	.013
IHC (0,1+ / 2+, 3+)	.958	NA	
IHC (0,1+,2+ / 3+)	.001	0.10 [0.02-0.64]	.015
SISH (negative / HP, NA)	.302	NA	