Human Pathology (2017) **64**, 98–105

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

# The gene copy number of c-MET has a significant impact on progression-free survival in Korean patients with ovarian carcinoma☆,☆☆

**Wook Youn Kim MD, PhD[a], Seung-Hyuk Shim MD[b], Ho Young Jung MD[a], Meari Dong MD[b], Soo-Nyung Kim MD, PhD[b], Sun Joo Lee MD, PhD[b,*]**

[a]*Department of Pathology, KonKuk University School of Medicine, Seoul, 05030 Republic of Korea*
[b]*Department of Obstetrics and Gynaecology, Konkuk University School of Medicine, Seoul, 05030 Republic of Korea*

Received 24 January 2017; revised 18 March 2017; accepted 2 April 2017

**Keywords:**
Ovarian carcinoma;
c-MET;
In situ hybridization;
Survival;
Gene copy number

**Summary** The aim of this study was to compare the protein overexpression and gene copy number (GCN) of c-MET in ovarian carcinoma and to assess their prognostic roles in Korean women. MET protein expression and GCN status were determined using immunohistochemistry (IHC) and silver in situ hybridization, respectively, in 105 ovarian carcinomas comprising 63 serous, 12 mucinous, 20 clear cell, and 10 endometrioid carcinomas. All cases had been treated and followed up at a single institute in Seoul, Korea. MET protein overexpression was observed in 35 of 105 (33.3%) ovarian carcinomas, with IHC 2+ in 27 and IHC 3+ in 8. The overexpression rates of serous, mucinous, clear cell, and endometrioid carcinomas were 14.3%, 83.3%, 65.0%, and 30.0%, respectively. MET protein overexpression was significant in mucinous carcinoma ($P < .001$) and was correlated with better progression-free survival (PFS) ($P = .028$). High polysomy (HP) of chromosome 7 and gene amplification (GA) were found in 10 (9.5%) and 2 (1.9%) of the 105 ovarian carcinomas, respectively. Eleven of 12 cases were high-grade serous carcinomas. The remaining case was clear cell carcinoma. HP and GA were associated with a poor PFS ($P = .001$). There was no significant correlation between a high level of protein expression and increased GCN of MET ($r = -0.127$, $P = .197$). In Korean women, HP and GA of *MET* were significantly correlated with a poor PFS. *MET* GCN may serve as a biomarker for poor prognosis in patients with ovarian carcinoma.


## 1. Introduction

Ovarian cancer is the 10th most common cancer in women in South Korea and was the 8th leading cause of death from cancer in 2013 [1]. Increasing evidence suggests that patients with various racial backgrounds may have different survival outcomes and histotype distributions. The age-standardized incidence and mortality rates in 2012 were 6.8 and 2.5, respectively, in Korea. In contrast, the age-standardized incidence and mortality rates in North America and northern Europe in 2012 were 8.1/5.0

☆ Competing interests: None of the authors has a conflict of interest to declare.

☆☆ Funding/Support: This study was sponsored by Hanmi Medicare, Seoul, Korea.

* Corresponding author at: Department of Obstetrics and Gynaecology, Konkuk University Hospital, Konkuk University School of Medicine, 120-1 Neungdong-ro, Hwayang-dong, Gwangjin-gu, Seoul, 05030, Republic of Korea.
*E-mail address:* lsj671121@gmail.com (S. J. Lee).

http://dx.doi.org/10.1016/j.humpath.2017.04.002
0046-8177/

and 11/5.9, respectively [2]. Clear cell carcinoma accounts for 10.3% of all ovarian carcinomas in Korea [3], whereas in Japan, for unknown reasons, this figure is >20% [4,5]. In Korea, serous carcinoma comprises 49.5% of all ovarian carcinomas [3]; however, worldwide, serous carcinoma comprises 75% to 80% of ovarian carcinomas [6]. In addition, Asians are more likely to have higher 5-year disease-specific survival [7].

MET, a receptor tyrosine kinase, is important in tumorigenesis and metastasis in a broad range of human malignancies [8,9]. *MET*, which is located on chromosome 7q31, encodes several functional domains, including a ligand-binding domain, a regulatory juxtamembrane domain, and a receptor tyrosine kinase domain [4,10]. Physiologically, upon binding of its ligand, hepatocyte growth factor (HGF, also known as *scatter factor*), the MET receptor undergoes dimerization and autophosphorylation at specific tyrosine residues within the cytoplasmic domain, thereby creating docking sites for intracellular signal transducers that activate Ras/mitogen-activated protein kinase, phosphatidylinositol 3-kinase, and signal transducers and activators of transcription signaling pathways [8,10]. MET is overexpressed in human ovarian cancers, and high levels of HGF have been found in ascites [11-13].

Although HGF has been known to allow the dispersal of cancer cells and possibly increase their invasiveness, a monoclonal antibody that targets HGF in women with recurrent or persistent ovarian carcinoma exhibited limited activity in a previous phase II study [9]. Moreover, the cases enrolled were serous and endometrioid carcinoma patients with persistent or recurrent disease, and MET status had not been investigated before treatment. According to another previous study, clear cell carcinomas frequently exhibit protein overexpression and copy number alterations of the *MET* gene compared with non–clear cell–type ovarian carcinomas in Japanese patients [4]. Anti-MET therapy that is given to properly selected patients is thought to show better results. Nonetheless, studies assessing a correlation between MET expression and prognosis in cancer are controversial [4,11,14-16]. Therefore, racial and histotype differences of *MET* gene copy number (GCN) alteration and MET expression in ovarian carcinomas require further study.

This study was designed to investigate the association between MET protein expression as evaluated using immunohistochemistry (IHC) and GCN as evaluated using silver in situ hybridization (SISH) in Korean patients with ovarian carcinoma. We also sought to determine whether MET status as determined using these 2 methods was associated with prognosis. This information may provide a new treatment method for Korean patients with ovarian carcinoma.

## 2. Materials and methods

### 2.1. Patients

The capital city of Korea, Seoul, is a "melting pot" of the Korean population. Most residents of Seoul have come from across the country or are their descendants. Our hospital has been a tertiary referral center for patients with cancer since August 2005. We reviewed all patients who were diagnosed as having ovarian carcinoma and who underwent standard treatment at Konkuk University Hospital, Seoul, South Korea, from August 2005 to August 2015. All treatments were performed based on National Comprehensive Cancer Network guidelines [17]. Patients were excluded from the analysis if any of the following criteria were met: (1) patients with mixed or undifferentiated carcinomas; (2) patients who had refused the recommended standard treatment. However, during the study period, there were no mixed or undifferentiated ovarian cancer cases. No cases refused the recommended standard treatment.

One hundred and five patients were enrolled in this study. Seventy-nine (75.2%) patients of the 105 resided within 20 minutes' travel time of the center, and the remaining patients came from various regions in Korea. The cases enrolled in this study are believed to be a representative sample of the Korean population. Three of the 105 patients underwent 3 cycles of neoadjuvant chemotherapy with paclitaxel-carboplatin before surgery. Neoadjuvant chemotherapy cases were confirmed pathologically before chemotherapy. A total of 102 patients who were treated with conventional standard therapy did not undergo chemotherapy or radiation therapy before surgery.

All specimens were formalin fixed and paraffin embedded, and the tumors were reviewed by 2 pathologists (W. Y. K. and H. Y. J.) and classified according to the criteria of the World Health Organization [18]. Clinicopathological details such as patient age, stage of disease, residual tumor after initial cytoreductive surgery, clinical response to chemotherapy, regional lymph node status, progression-free survival (PFS), and overall survival (OS) were assessed. Residual disease <1 cm was defined as *optimal cytoreduction* [17]. *PFS* was defined as the duration from the date of initial treatment to disease progression or death from any cause. *OS* was defined as the duration from the date of initial treatment to the date of either the last follow-up or death. Surgical stages were revised according to the 2014 International Federation of Gynecology and Obstetrics (FIGO) staging system. Clinical response to therapy was evaluated using computed tomography and tumor markers and was reclassified as complete response, partial response, stable disease, or progressive disease according to the revised Response Evaluation Criteria for Solid Tumors guidelines [19]. Follow-up was calculated from the date of initial treatment to the date of either the last follow-up or death. Sixteen (15.2%) of 105 patients died because of their tumor burden during the study period.

This study was approved by the institutional review board at Konkuk University Hospital.

### 2.2. Tissue samples and construction of tissue microarray

The tissue microarray (TMA) was manufactured using representative tissue samples from 105 ovarian carcinomas.