

Prognostic impact of epithelial cell adhesion molecule in ovarian cancer patients

To the editor: Epithelial cell adhesion molecule (EpCAM) was originally discovered in 1979, then, subsequent studies identified that EpCAM is a type I transmembrane glycoprotein that acts as an epithelial-specific cell-adhesion molecule [1]. Although the precise function of EpCAM remains largely unknown, its role is not limited to cell adhesion as it is also involved in cellular signaling, cell migration, proliferation, and differentiation [2].

With interest we read the recently published article by Woopen et al [3]. They report that EpCAM overexpression is associated with more favorable survival and higher response rates to platinum based chemotherapy of 74 epithelial ovarian cancer patients. However, EpCAM expression did not correlate with tumor stage, grade, lymph node metastasis, distant metastasis or tumor residuals. This result is apposite results with overexpression of the EpCAM in ovarian tumors would promote shedding of tumor cells and thus correlate with an unfavorable outcome, was reported in previous studies [4,5]. This discrepancy may be due to that the authors only partly analyzed using immunohistochemical staining to estimate EpCAM expression. More highly standardized staining conditions on tissue microarrays by frequency, intensity, and homogeneity of EpCAM expression are needed in a future study. Moreover, the analysis of early stage ovarian cancer was based on 14 patients only and more care should be taken to conclude on overall survival. Lastly, in multivariate analysis of prognostic factors for overall survival, tumor stage is not significant in this study. This is surprising when considering the tumor stage is regarded as the most important prognostic factors along with residual tumor after initial surgery.

It is questionable why EpCAM expression was negative in some tumor types when it was mostly neutral in other tumor types which bears prognostic impact on overall survival.

EpCAM expression was negatively correlated with survival as previously observed for breast, gall bladder, pancreas, and squamous cell carcinoma of head and neck cancer [6,7]. On the contrary, in patients with early gastric cancer, clear cell renal cancer, non-small cell lung cancer, there are positive impacts on overall survival [8,9].

The prognostic role of EpCAM expression in certain carcinomas provide a strong basis for further investigating anti-EpCAM targeted therapies. In 2009, the first EpCAM targeting antibody, the trifunctional anti-EpCAM, anti-CD3 antibody catumaxomab (Removab, Fresenius Biotech GmbH, Munich, Germany) received European market approval for intraperitoneal treatment of malignant ascites in patients with EpCAM positive carcinomas where standard therapy is not available. Catumaxomab showed a clear clinical benefit and an acceptable safety profile in patients with malignant ascites [10,11]. Another possible further role in carcinogenesis may be the involvement of the EpCAM antigen in immunosuppressive processes by blocking MHC class II-dependent antigen presentation [12].

Despite the overexpression of EpCAM on cancer cells, its impact on tumor progression is still controversial. A future research will provide detailed understanding of EpCAM signaling in the nucleus, the regulation of EpCAM signaling as may be controlled via interaction of EpCAM with itself and other proteins in the plasma membrane, the expression and role of EpCAM on normal and cancer stem cells, and the study of clinical efficacy of a number of EpCAM-directed immunotherapies.

Recently, a variety of biomarker has been proposed as potential candidates for molecular-targeted therapy. Original and translational research are strongly recommended to improve the knowledge in this field and to identify reliable and validated biomarker that could offer the best therapy for each patient in order to achieve the highest clinical benefit with the lowest drug-related toxicity.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Baeuerle PA, Gires O. EpCAM (CD326) finding its role in cancer. *Br J Cancer* 2007;96:417-23.
2. Patriarca C, Macchi RM, Marschner AK, Mellstedt H. Epithelial cell adhesion molecule expression (CD326) in cancer: a short review. *Cancer Treat Rev* 2012;38:68-75.
3. Woopen H, Pietzner K, Richter R, Fotopoulou C, Joens T, Braicu EI, et al. Overexpression of the epithelial cell adhesion molecule is associated with a more favorable prognosis and response to platinum-based chemotherapy in ovarian cancer. *J Gynecol Oncol* 2014;25:221-8.
4. Bellone S, Siegel ER, Cocco E, Cargnelutti M, Silasi DA, Azodi M, et al. Overexpression of epithelial cell adhesion molecule in primary, metastatic, and recurrent/chemotherapy-resistant epithelial ovarian cancer: implications for epithelial cell adhesion molecule-specific immunotherapy. *Int J Gynecol Cancer* 2009;19:860-6.
5. Spizzo G, Went P, Dirnhofer S, Obrist P, Moch H, Baeuerle PA, et al. Overexpression of epithelial cell adhesion molecule (Ep-CAM) is an independent prognostic marker for reduced survival of patients with epithelial ovarian cancer. *Gynecol Oncol* 2006;103:483-8.
6. Spizzo G, Went P, Dirnhofer S, Obrist P, Simon R, Spichtin H, et al. High Ep-CAM expression is associated with poor prognosis in node-positive breast cancer. *Breast Cancer Res Treat* 2004;86:207-13.
7. Varga M, Obrist P, Schneeberger S, Muhlmann G, Felgel-Farnholz C, Fong D, et al. Overexpression of epithelial cell adhesion molecule antigen in gallbladder carcinoma is an independent marker for poor survival. *Clin Cancer Res* 2004;10:3131-6.
8. Went P, Dirnhofer S, Salvisberg T, Amin MB, Lim SD, Diener PA, et al. Expression of epithelial cell adhesion molecule (EpCam) in renal epithelial tumors. *Am J Surg Pathol* 2005;29:83-8.
9. Went P, Vasei M, Bubendorf L, Terracciano L, Tornillo L, Riede U, et al. Frequent high-level expression of the immunotherapeutic target Ep-CAM in colon, stomach, prostate and lung cancers. *Br J Cancer* 2006;94:128-35.
10. Heiss MM, Murawa P, Koralewski P, Kutarska E, Kolesnik OO, Ivanchenko VV, et al. The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: results of a prospective randomized phase II/III trial. *Int J Cancer* 2010;127:2209-21.
11. Ott MG, Marme F, Moldenhauer G, Lindhofer H, Hennig M, Spannagl R, et al. Humoral response to catumaxomab correlates with clinical outcome: results of the pivotal phase II/III study in patients with malignant ascites. *Int J Cancer* 2012;130:2195-203.
12. Gutzmer R, Li W, Sutterwala S, Lemos MP, Elizalde JI, Urtishak SL, et al. A tumor-associated glycoprotein that blocks MHC class II-dependent antigen presentation by dendritic cells. *J Immunol* 2004;173:1023-32.

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<http://dx.doi.org/10.3802/jgo.2014.25.4.352>

Reply to M Lee

Thank you very much for your interest in our recently published article “Overexpression of the epithelial cell adhesion molecule is associated with a more favorable prognosis and response to platinum-based chemotherapy in ovarian cancer” [1]. We could identify epithelial cell adhesion molecule (EpCAM) as independent prognostic marker for overall survival and could show that EpCAM overexpression is associated with a better progression free survival and higher response rates to platinum-based chemotherapy.

Interestingly, Battista et al. published very similar results in April this year. EpCAM was—in concordance to our results—found to be associated with a favorable prognosis in ovarian cancer in their analysis [2]. They assessed EpCAM expression by an immunoreactive score consisting of both a proportion score and an intensity score as earlier described by Spizzo et al. [3]. This is why we do not think that the discrepancy of results to Spizzo et al. who showed an association of EpCAM with reduced survival can be explained with different methods as stated in the letter to the editor. We rather believe that these contradictory results of EpCAM as prognostic marker may reflect the ambiguous functional roles of EpCAM—being on the one hand a cell-adhesion molecule and on the other hand playing a role in tumor proliferation and differentiation [4].

Addressing the concern of the lacking association of EpCAM with other prognostic markers our results are in line with Battista et al. who could also not demonstrate an association of EpCAM overexpression with tumor stage, grading and postoperative tumor residuals [2]. Spizzo et al. [3] failed to show an association with tumor stage either – they could only show an association with grading.

One concern of the author of the letter to the editor was the small amount of early ovarian cancers. As we are a university center specialized in gynecologic oncology with focus on ovarian cancer we especially treat patients with more advanced tumor stages (International Federation of Gynecology and Obstetrics [FIGO] III/IV) which might explain the high amount of advanced ovarian cancers in our collective (> 82% FIGO III/IV) in contrary to Battista et al. whose collective included approximately 76% FIGO III/IV cases and Spizzo et al with about 71% of advanced stages [2,3].

We agree that larger studies are warranted in order to further understand the function and possible roles of EpCAM in oncology. We believe that EpCAM might be a very interesting

therapeutic target in the future as already demonstrated with the EpCAM-targeting Catumaxomab which is EMA-approved for the treatment of malignant ascites in EpCAM-positive tumors [5].

CONFLICT OF INTEREST

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REFERENCES

1. Woopen H, Pietzner K, Richter R, Fotopoulou C, Joens T, Braicu EI, et al. Overexpression of the epithelial cell adhesion molecule is associated with a more favorable prognosis and response to platinum-based chemotherapy in ovarian cancer. *J Gynecol Oncol* 2014;25:221-8.
2. Battista MJ, Cotarelo C, Jakobi S, Steetskamp J, Makris G, Sicking I, et al. Overexpression of epithelial cell adhesion molecule protein is associated with favorable prognosis in an unselected cohort of ovarian cancer patients. *J Cancer Res Clin Oncol* 2014;140:1097-102.
3. Spizzo G, Went P, Dirnhofer S, Obrist P, Moch H, Baeuerle PA, et al. Overexpression of epithelial cell adhesion molecule (Ep-CAM) is an independent prognostic marker for reduced survival of patients with epithelial ovarian cancer. *Gynecol Oncol* 2006;103:483-8.
4. van der Gun BT, Melchers LJ, Ruiters MH, de Leij LF, McLaughlin PM, Rots MG. EpCAM in carcinogenesis: the good, the bad or the ugly. *Carcinogenesis* 2010;31:1913-21.
5. Heiss MM, Murawa P, Koralewski P, Kutarska E, Kolesnik OO, Ivanchenko VV, et al. The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: Results of a prospective randomized phase II/III trial. *Int J Cancer* 2010;127:2209-21.

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<http://dx.doi.org/10.3802/jgo.2014.25.4.354>

