High Endothelial Venule with Concomitant high CD8+ T-cell Infiltration is Associated with a Favorable Prognosis in Resected Gastric Cancer

Soon Auck Hong¹, Hye Won Hwang¹, Min Kyoong Kim², Tae Jin Lee¹, Kwangil Yim³, Hye Sung Won⁴, Der Sheng Sun⁴, Eun Young Kim⁵ and Yoon Ho Ko⁴,⁶*

¹Pathology, College of Medicine, Chung-Ang University, Korea ²Surgery, Chung-Ang University Hospital, College of Medicine, Chung-Ang University, Korea ³Hospital Pathology, Uijeongbu St. Mary’s Hospital, College of Medicine, Korea ⁴Division of Medical Oncology, Department of Internal Medicine, College of Medicine, Catholic University, Korea ⁵Surgery, Uijeongbu St. Mary’s Hospital, College of Medicine, Catholic University, Korea ⁶Cancer Research Institute, College of Medicine, The Catholic University, Korea
Background/Aims

- CD8$^+$ tumor infiltrating lymphocytes (TILs) are main effector for antitumor immunity.
- High endothelial venules (HEVs) are related with diverse immune cells in solid tumors.
- In this study, we analysed CD8$^+$ and Foxp3$^+$ TILs combined with HEV and tend to find the prognostic role in advanced gastric cancer.
Methods

• 157 patients with AGC were enrolled in this study.
• The density of CD8+ TIL and Foxp3+ TIL were calculated with immunohistochemical staining.
• HEV was evaluated by MECA-79 expression.
• The mean number of CD8+ and Foxp3+ TILs are calculated by manually. MECA-79 expression was evaluated on endothelial cell of vessels in intratumoral and peritumoral stroma.
• The cut value for high and low expression was defined as median value of CD8+ and Foxp3+ TILs.
• A positivity for MECA-79 in any number of vessels was defined as the presence of HEV
Results

Table 1. Correlation between CD8+, Foxp3+ TILs, HEV, and clinicopathologic findings of advanced gastric cancer

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<th>CD8+</th>
<th>Foxp3+ TILs</th>
<th>HEV</th>
<th>Clinicopathologic Findings</th>
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Table 2. Association between high CD8 with positive MECA-79, high CD8/FOXP3 with positive MECA-79, and clinicopathologic finding of advanced gastric cancer.

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<th>CD8+</th>
<th>MECA-79</th>
<th>CD8/FOXP3</th>
<th>MECA-79</th>
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Results

Table 3. Univariate and multivariate analyses of factors associated with overall survival of advanced gastric cancer
Results

Figure 1. Representative immunohistochemistry of CD8+ tumor infiltrating lymphocytes (TILs), Foxp3+ TILs, and MECA-79 expression. (A) high CD8+ TIL, (B) low CD8+ TIL, (C) high Foxp3+ TIL, (D) low Foxp3+ TIL, (E) high endothelial venules (HEV) exhibited by MECA-79, (F) no HEV identified by MECA-79.

Figure 2. Differences between CD8+ Tumor infiltrating lymphocytes (TILs) and Foxp3+ TIL according to the presence or absence of high endothelial venules (HEV). (A) significant elevation of CD8+ TIL in HEV positive patients, compared to HEV negative patients (P=0.027), (B) a non-significant increase in the density of Foxp3+ TIL in HEV positive cases as compared to HEV negative cases (P=0.455).
Figure 3. Prognostic effects for combined analysis of CD8+ tumor infiltrating lymphocytes (TILs) and high endothelial venule (HEV). (A) patients with high CD8+ TILs and HEV demonstrated a higher overall survival (OS) as compared to other groups (P=0.015), (B) in the group with high CD8+TILs HEV are associated with significantly favorable OS, (C) OS differences are not observed between patients with/without HEV in the low CD8+TIL group.
Conclusion

• This study highlights the prognostic role of HEV and TILs in advanced GC.
• HEV is significantly associated with high CD8+TILs, while it is not affected by Foxp3+TILs in GC.
• HEV itself does not impact survival.
• A subgroup analysis demonstrated that high CD8+TIL with HEV demonstrated a favorable prognosis and was an independent prognostic factor in advanced GC.
• Further research for the interaction between CD8+TIL and HEV is needed to better understand the tumor microenvironment in AGC.