Background: The prognosis of advanced esophageal squamous cell carcinoma (ESCC) is extremely poor. With an increasing potential of immune checkpoints modulators in oncology, the aim of the current study was to assess the extent of tumor infiltrating lymphocyte (TIL) and expression and significance of various immune checkpoints in the resected ESCC.

Methods: Total 396 patients who underwent radical surgery for ESCC between 2005 and 2013 were included. Using immunohistochemistry (IHC) with tissue microarray, type of T-cells including CD3, CD8, and FoxP3 T-cell and the expression of checkpoints including programmed cell death ligand 1 (PD-L1), programmed cell death-1 (PD-1), inducible co-stimulator (ICOS), lymphocyte activation gene-3 (LAG-3), and T-cell immunoglobulin and mucin-dominant containing-3 (TIM-3) was manually scored. Outcome measures included recurrence-free survival (RFS) and overall survival (OS). The expression was defined as high density when the expression level was above the median value/4 HPFs (high-power fields).

Results: With median follow-up period of 24.8 months, 32.6% of recurrence and 45.7% of death occurred. Patients with a high frequency of CD3+ TILs (n = 198) demonstrated a significant longer RFS (hazard ratio [HR] = 0.61, P = 0.0095) and OS (HR = 0.59, P = 0.0005). High ICOS expression group (n = 184) displayed longer RFS (HR = 0.72, P = 0.021) and OS (HR = 0.67, P = 0.007) than low ICOS expression group. Regarding PD-1 expression, the RFS (HR = 0.67, P = 0.004) and OS (HR = 0.66, P = 0.006) were significantly better in high expression group (n = 179). In multivariate Cox analyses, high CD3+ TIL and ICOS were also indicated as an independent prognostic factor for better RFS (HR = 0.59, P < 0.001 and HR = 0.64, P = 0.002, respectively) and OS (HR = 0.48, P < 0.001 and HR = 0.66, respectively) and high TIM-3 expression in immune cells was related to the shorter RFS (HR = 1.46, P = 0.020) and OS (HR = 1.54, P = 0.013). Even though various cut-off applied, the expression of PD-L1 in tumor or immune cells failed to report any association with prognosis.

Conclusions: Our analysis involving TMA and IHC of multiple immune checkpoints in resected ESCC suggests that CD3+ TILs and ICOS+ T-cells might be a favorable prognostic factor.

Legal entity responsible for the study: Min Hee Hong.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.