Better survival following Helicobacter pylori infection

~Host immune response to advanced gastric cancer~

A research group led by Satoshi Nishizuka, MD, PhD at Iwate Medical University Institute for Biomedical Sciences announces that, paradoxically, *H. pylori* infection contributes to a better survival rate among advanced gastric cancer patients, implying an enhanced host immune response. The research on 658 advanced gastric cancer patients was spearheaded by an MD-PhD student, Yuka Koizumi of the Nishizuka laboratory, in an international collaborative setting including 12 institutions from the Northern Japan Gastric Cancer Consortium and the Center for Applied Proteomics and Molecular Medicine, at George Mason University.

Youtube link: https://www.youtube.com/watch?v=aXqMSY78LkU

Highlights

>The current standard-of-care for advanced gastric cancer therapy is gastrectomy (removing the stomach) and chemotherapy. The research group conducted an investigation including patients who received only surgery, so that the effect of chemotherapy could be rigorously evaluated.

>The results show for the first time that the combinational index of immune evasion, Programmed Death-Ligand1(PD-L1) expression level, and *H. pylori* infection may predict treatment efficacy in advanced gastric cancer patients.

Background

Recent progress in advanced gastric cancer treatment has improved survival rates; however, it remains to be solved how to predict high-risk groups, in terms of recurrence (i.e., a cancer once treated that comes back). While gastric cancer treatment differs by country/region, investigators from several countries have reported that patients with *H. pylori* infection showed a better survival rate. A previous study focusing on Japanese patients has also revealed that patients who were *H. pylori*-positive showed a better survival rate than those with a negative status (Nishizuka et al, J Surg Oncol, 2018). *H. pylori* has been known as a cause of gastritis (i.e., inflammation of the stomach), but it is worth noting that a majority of *H. pylori*-positive individuals eventually do not develop cancer. Furthermore, the number of deaths caused by gastric cancer had begun to decrease even before eradication therapy was widely applied (for gastritis patients). This suggests that *H. pylori* may not be a direct cause of gastric cancer-related deaths (cancer statistics in Japan, 2021 provided by ganjoho.jp). We

hypothesized that the observed better survival of gastric cancer may have been caused by an *H. pylori* infection-modulated host's immune response. In the present study, based on this hypothesis, we performed a rigorous statistical analysis with a multiple immune response index of the 658 gastric cancer specimens from the Northern Japan Gastric Cancer Consortium.

Methods

The study subjects were 658 advanced gastric cancer cases who received a gastrectomy in between 2009 and 2013 at one of the 12 institutes participating in the Northern Japan Gastric Cancer Consortium. A previous study on this cohort revealed that patients who were *H. pylori*-positive had a statistically better survival rate than those who were *H. pylori*-negative (Figure 1). In the present study, to assess the mechanism yielding better survival rates, we evaluated clinicopathological parameters in addition to *H. pylori* infection status, including PD-L1 expression level and lymphocyte infiltration index, age, sex, treatment, and staging.

Results

A combinatory analysis of clinicopathological and immunohistochemical indices based on *H. pylori* infection status revealed that the *PD-L1 expression level* and *dose of S-1* (an anticancer agent) had a statistical interaction with relapse-free survival (Figure 2). By narrowing the subject to those with both *PD-L1-negative* and *received S-1 chemotherapy* status, the 5-year relapse-free survival rate was 28% higher in patients who were *H. pylori*-positive than those who were *H. pylori*-negative (Figure 3). Furthermore, even those in the dose-reduced S-1 chemotherapy group (i.e., who we assumed had a poor prognosis) demonstrated a higher survival rate if they were *H. pylori*-positive than if they were *H. pylori* -negative (Figure 4).

Conclusion

These results suggest that *H. pylori* better modulates host immunity in advanced gastric cancer patients when the patient is *H. pylori*-positive and PD-L1-negative.

Prospective

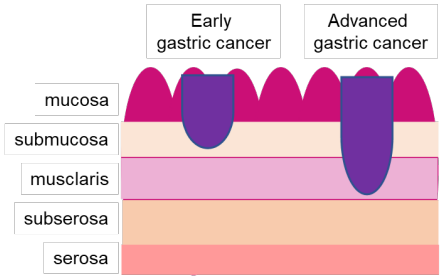
The combination of *H. pylori* infection status and PD-L1 expression level may assist in the selection of anticancer agents and the determination of appropriate doses of the agents.

Glossary

1 Immune evasion (of cancer cell): A status for cancer cells not being attacked byhost immune cells achieved by releasing substance or expressing proteins.

2 PD-L1: A cell membrane protein on a cancer cell membrane binds to a protein, PD-1, that is expressed on immune cells. The binding induces an immune evasion mechanism.

3 Advanced gastric cancer: The gastric wall is comprised of the following five layers, from inside out: mucosa, submucosa, muscularis, subserosa, and serosa. According to *Japanese Classification of Gastric Carcinoma* (15th edition), depth can classify early and advanced cancers. An early cancer is one where the cancer's invasion is limited to the submucosal layer, whereas the invasion in an advanced cancer goes beyond the muscular layer. See below.



4 (post-operative) Adjuvant chemotherapy: A chemotherapy whose objective is to suppress recurrence by minimum residual diseases. It is performed after surgery with a curative intent.

5 Survival curves: A graph displaying fractions of events (which can happen only once, such as death) happening according to time. In cases where the event is death in two groups, a hazard ratio can be calculated based on the two survival curves.

6 Interaction (statistics): An effect that occurs when one variable depends on another variable.

Original paper

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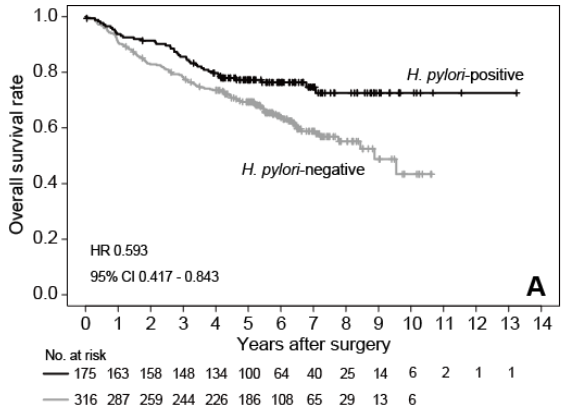

Figure 1: Overall survival of *H. pylori*-positive and -negative gastric cancer patients.
Five-year overall survival after gastrectomy is 7.9% higher in *H. pylori*-positive patients than those with a negative status. In the following year, the survival rate difference grows wider (Nishizuka et al, *J Surg Oncol*, 2018).

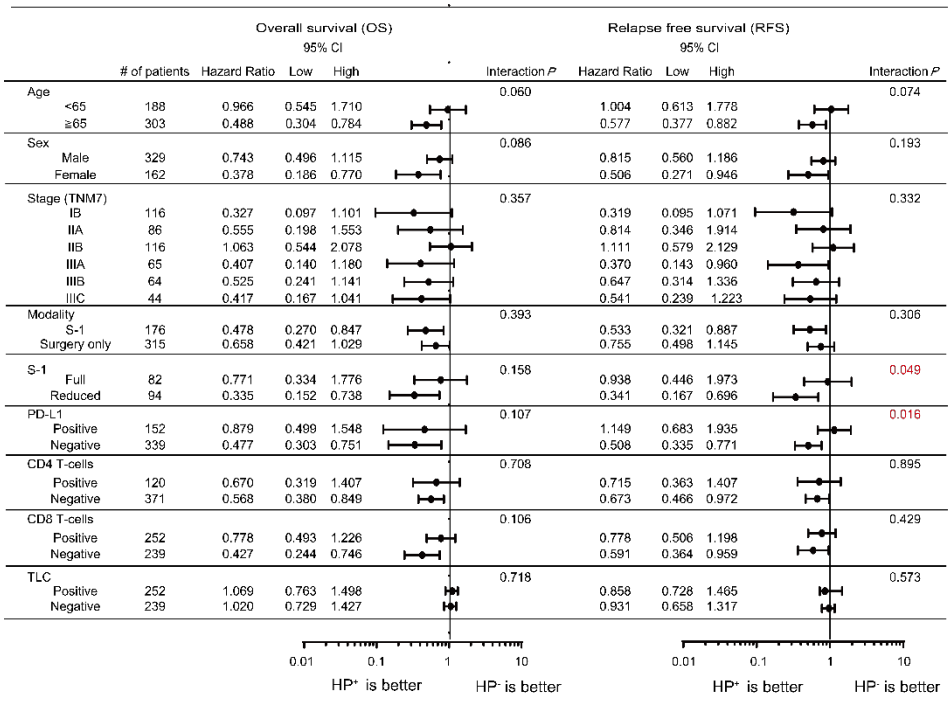

Figure 2: Subgroup analysis stratified based on survival and clinicopathological/immunological parameters in terms of *H. pylori* infection status.
PD-L1 level and S-1 dose showed an interaction with *H. pylori* infection status. See *P*=0.049 and *P*=0.016, in red.

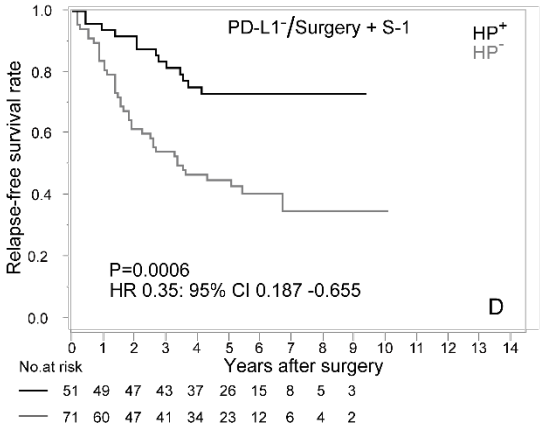

Figure 3: Relapse-free survival rate of PD-L1(-)/Surgery + S-1 group patients.

Patients who received S-1 chemotherapy and who do not express PD-L1 showed a better survival rate in those patients with *H. pylori*-positive status than those with a negative status.

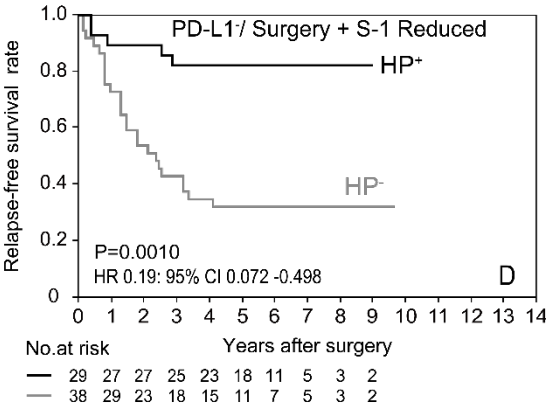

Figure 4: Relapse-free survival rate of PD-L1(-)/Surgery + S-1 reduced group patients.

Patients who received dose-reduced S-1 chemotherapy also do not express PD-L1. They showed a better survival rate if they were *H. pylori*-positive than those with a negative status.