Gastric Cancer Treatment in Japan

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Ask the Experts

What is the trend in the incidence and death from gastric cancer in the Japanese population? How does this compare to the age standardized incidence rate of gastric cancer in the world?

Gastric cancer in Japan was ranked as the most common cancer in the past, but this aspect has gradually been changing in recent years. In 1999, the leading cause of cancer death from gastric cancer was overtaken by that of lung cancer in men and colorectal cancer in women (1). The incidence of gastric cancer continues to be still highest among all cancers. Although age-standardized incidence and death rates have been declining for decades, the absolute number of gastric cancer cases have been showing an increasing trend. The data from Cancer Incidence in Five Continents (2) show that the annual age-standardized incidence rate in Japanese cancer registries ranges from 50 to 80 per 100,000 among men and from 20 to 30 per 100,000 among women. These data on gastric cancer are much higher than the other countries in the world.

How is the screening for gastric cancer performed in Japan?
In Japan, mass screening for gastric cancer is performed with photofluography. This procedure began in 1960, and to date, over 6 million people have been screened annually. The five year survival rate is 15% better in screen-detected cancers than in symptom-diagnosed cases, though no randomised controlled trials have been reported (3). As an alternative screening method, the measurement of serum pepsinogens has recently been introduced for gastric cancer, but there is no evidence that the measurement of pepsinogens reduces gastric cancer mortality (3).

How are gastric cancer patients currently tested in Japan for HER2-positivity - given the fact that trastuzumab is not yet approved in Japan? How will this change after trastuzumab is approved in Japan?
Since trastuzumab has not been approved in Japan yet, we do not know the number of pathologists who will be involved in the HER2-IHC and HER2-FISH.

If trastuzumab is approved in Japan, the “Japanese Pathology Board for Optimal Use of Trastuzumab in Gastric Cancer” plans to standardize the diagnosis of HER2-positivity by providing and distributing an atlas that describes the criteria of HER2 testing using various antibodies as well as the use of HER2-FISH in gastric cancer.

How many pathologists are involved in the immunohistochemical and FISH analysis of HER2-positivity for gastric cancer in Japan?
Since Heceptin has not been approved in Japan yet, we do not know the number of pathologists who will be involved in the HER2-IHC and HER2-FISH.

How much concordance do you get between HER2-IHC and HER2-FISH with respect to gastric cancer samples?
The concordance rate between HER2-IHC and HER2-FISH in surgically resected tumor samples has been shown to be 86.9%. These results were obtained from a study of 200 gastric cancer cases that was published in Oncology Report in 2006 (4).
What are the targeted therapies used or are being considered for use in Japan and what testing is done to qualify patients for these therapies?

We do not have any molecular-targeted therapies approved by the Ministry of Health, Labor and Welfare of Japan for gastric cancer. However, several clinical studies using including molecular-targeted drugs for gastric cancer are undergoing to study the efficacy of the treatment.

Is the clinical significance of HER2 amplification in gastric cancer and over-expression fully clear?

Some studies reported that there is no significance between HER2 over-expression and patients outcome in surgically resected cases (5, 6). We have no data concerning the impact of HER2 amplification or over-expression on the patients’ response to the chemotherapy in gastric cancer. We will plan to investigate these two parameters.

Is there an association between HER2 and poor prognosis in gastric cancer?

Previously our data (4) indicated that there was no significant survival difference between HER2-positive and HER2-negative gastric cancer cases. Now we are planning to study the relationship between HER2 status and clinicopathology, response to chemotherapy, and patient’s prognosis.

In general, what is the rate of HER2-positivity in gastric cancer patients?

Our previous data (4) indicated the rate of HER2-positivity in gastric cancer to be around 20%. This positive immunoreactivity was frequently observed in differentiated or intestinal-type of gastric cancer. The HER2-positivity rate of gastric cancer ranged from 20% to 40% of the total gastric cancer in ToGA study.

Why is tumor heterogeneity more common in gastric cancer than breast cancer?

Histological heterogeneity is one of the most characteristic feature of gastric cancer compared to breast cancer. It is well known that there are two major histological subtypes of gastric cancer; intestinal and diffuse. These two histological types of gastric cancers possess different profiles of genetic alterations indicating different etiology of these cancers (7). However, in a tumor of either histological subtype, histological heterogeneity is still common in the gastric cancer. This may be due to either variation in protein expression or changes in gene mutations, though it is not clear why the tumor heterogeneity is more common in gastric cancer than breast cancer.

What is your experience with respect to protein expression and gene amplification of HER2 in gastric cancer?

Our previous data (4) indicated that the concordance rate of HER2 protein expression and gene amplification detected by FISH in gastric cancer is 86.9% in surgical materials.

In what way will the results of the ToGA trial lead to changes in the medical practice for gastric cancer in Japan?

The results of the ToGA trial clearly indicates the usefulness of trastuzumab in HER2-positive gastric cancer patients. The data from this trial will provide many alternative treatment methods for gastric cancer patients, such as adjuvant treatment, neoadjuvant treatment and combination with other molecular targeted therapies, as well as standard chemotherapy.

Are there any differences in the scoring criteria for HER2 over-expression in gastric cancer and breast cancer?

There are some differences in the scoring criteria for HER2 expression between gastric and breast cancer, as reported by Hoffman, et al. (8). IHC positive (3+) in gastric cancer is defined as moderate to strong or basolateral membraneous (U shaped) reactivity in more than 10% of cancer cells. The definition for FISH criteria that HER2:CEP17 ratio is more than 2, is also applied for gastric cancer, which is the original criteria for breast cancer.

Do you find any differences in the HER2 over-expression/amplification when you analyze tissue from the GE junction and the stomach?

We have not obtained any data about the difference in the HER2 over-expression/amplification in the GE junction and the stomach cancers. Although the number of GE junctional cancer have increased in Japan, the total number is still low. Japanese GE junctional cancer cases will be collected by a multicenter study and the results of the ToGA study will be confirmed.

Is it true that the accuracy of the diagnosis increases with the number of biopsies taken from each lesion? What are the procedures for taking biopsies in Japan?

Accuracy of the diagnosis may not be defined by the number of biopsies taken from each lesion, but by the accuracy of detection of tumor by endoscopists. Recent advances of endoscopic techniques, as well as diagnostic procedures, e.g., magnifying endoscopy, narrow band endoscopy, and counter-staining procedures, have helped the endoscopists to find tumor area more easily and precisely in Japan.
**H&E Staining.** Morphological heterogeneity of gastric cancer. Differentiated adenocarcinoma showing ductal structure and poorly differentiated adenocarcinoma are mixed. Black arrow: Differentiated adenocarcinoma showing ductal structure, Blue arrow: Poorly differentiated adenocarcinoma.

**IHC Staining.** HER2 expression in gastric cancer. HER2 over-expression in well differentiated adenocarcinoma. Stained by Dako HercepTest™ Kit K5204.
Anatomy of the Stomach

References