# Plasma Chromogranin A Levels Predict Survival and Tumor Response in Patients with Advanced Gastroenteropancreatic Neuroendocrine Tumors

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**Abstract.** *Aim: To correlate the baseline and change of chromogranin A (CgA) levels with patient survival and tumor response in Asian patients with advanced gastro-enteropancreatic neuroendocrine tumors (GEP-NETs). Patients and Methods: Sixty patients with advanced GEP-NET treated in a medical center between April 2010 and April 2013 were enrolled retrospectively. Plasma CgA level was analyzed for correlation with the patient's clinical outcome and tumor response. Results: Multivariate analysis showed that independent favorable prognostic factors for overall survival were: Eastern Cooperative Oncology Groups performance score 0-1, World Health Organization tumor grade 1-2, single organ metastasis and less than twice the upper normal range of baseline CgA levels. Percentage changes in paired CgA tests (ΔCgA) of more than 17% can predict partial response or stable disease from progressive disease with 91.2% sensitivity and 82.9% specificity. Conclusion: Baseline plasma CgA levels predicted overall survival and ΔCgA predicted treatment response in Asian patients with GEP-NETs.*

Plasma chromogranin A (CgA) is one of the most commonly evaluated biomarkers in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) (1-7). CgA protein is expressed by pan-neuronal cells and is co-secreted with endocrine hormones during exocytosis of secretory granules by neuroendocrine cells (8); therefore, CgA expression correlates with neuroendocrine cell activity (9). CgA is elevated in 60-80% of patients with GEP-NETs (10). The CgA level has been reported to differentiate patients with GEP-NETs from healthy controls with 53-86% sensitivity and 84-98% specificity (2-7, 11), and CgA was significantly more accurate for diagnosis of NETs than other common NET biomarkers such as urine 5-hydroxyindoleacetic acid, neuron-specific enolase, and pancreatic polypeptide (3, 10-12).

In addition to its diagnostic value, plasma CgA is widely established as being useful for evaluating tumor status and predicting patient outcome. The correlation between plasma CgA levels and tumor burden in patients with midgut NETs and the shorter survival of patients with high initial plasma CgA levels were first reported by Janson *et al*. (13) in 1997 and were supported by three additional reports (14-16). However, Khan *et al*. reported that plasma CgA level correlated with overall survival in a univariate analysis but did not significantly predict overall survival after multivariate analysis of 175 patients with pulmonary or GEP-NETs (17). Furthermore, Massironi *et al*. reported that elevation of the baseline plasma CgA levels by more than 1-fold over the upper normal level (UNL) correlated significantly with the World Health Organization (WHO) tumor grade and clinical stage, but did not predict overall survival (18). In summary, the prognostic value of plasma CgA in patients with GEP-NETs requires further investigation.

The European Society for Medical Oncology (ESMO) guidelines recommend complementing imaging procedures with biochemical analysis (such plasma CgA measurement) for monitoring during treatment and follow-up of patients with GEP-NETs (19). Baudin *et al*. first reported changes in serial plasma CgA levels in a patient with non-functional pancreatic NET with progressive liver metastases (10). Yao *et*

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*al*. reported that an early plasma CgA response (defined as a ≥30% decrease or normalization by week 4) predicted better progression-free and overall survival in patients with advanced pancreatic NETs treated with everolimus (15). Korse *et al*. reported that changes in the plasma CgA level in serial samples correlated significantly with changes in the levels of physical function and global quality of life in patients with GEP-NETs during treatment with a long-acting sandostatin analog (16). However, beyond the prediction of patient outcome and quality of life under selected treatment regimens, the clinical value of serial plasma CgA measurements in patients with GEP-NETs is unclear.

Our previous report suggested that the plasma CgA level is a reliable biomarker for identifying patients with advanced/metastatic GEP-NETs in an Asian population and the changes of consecutive plasma CgA levels were associated with treatment response in 11 patients with GEP-NETs (20). Because we were limited by patient numbers and few data of serial plasma CgA measurements after tumor treatment, we were unable to address the prognostic and predictive value of plasma CgA level in our previous report. The present study aimed to elucidate the importance of baseline plasma CgA levels and the significance of changes in consecutive plasma CgA levels in terms of treatment response in Asian patients with advanced GEP-NETs.

## Patients and Methods

The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital(IRB No 99-1645B) . Written informed consent to participate was obtained from all patients. Sixty consecutive patients with a histological diagnosis of GEP-NETs treated at Chang Gung Memorial Hospital between April 2010 and April 2013 were enrolled retrospectively. All patients underwent a baseline evaluation that included clinical history, imaging studies, and biochemical evaluation. Imaging studies included sonography, computed tomography (CT), and magnetic resonance imaging (MRI) of the abdomen, as well as esophagogastroduodenoscopy or colonofibroscopy. All patients had advanced/metastatic disease confirmed by imaging studies. The patients' demographic data, tumor stage, pathological grade, and response to treatment were collected. Tumor grade was classified according to the World Health Organization 2010 definition (21) according to Ki67 index. Treatment strategies included surveillance or systemic antitumor therapy. Systemic antitumor therapy consisted of a somatostatin analog, a targeted agent (sunitinib or everolimus), and cytotoxic chemotherapy. Patients who received a somatostatin analog were treated long-term with intramuscular injection of octreotide long-acting release 20-30 every 28 days (Sandostatin long-acting release; Novartis). A targeted agent or cytotoxic chemotherapy in combination with somatostatin analog was administrated for patients with progressive disease (PD) after somatostatin analog treatment. A functional tumor was defined as a tumor secreting sufficient hormone to cause clinical symptoms. Patients with NETs rather than GEP origin, with multiple endocrine neoplasia type 1 disease, lack of plasma CgA measurement, or who received local ablation therapy for metastatic GEP-NET during the enrolled period were excluded from this study. All patients were followed-up until October 31, 2013.

*Measurement of plasma CgA*. Blood samples were obtained after overnight fasting and collected at baseline and at regular intervals after antitumor therapy. As a kit for measurement of plasma CgA became available in Taiwan in April 2010, the baseline CgA was defined as the measurement made at the beginning of the study in patients who were diagnosed with GEP-NETs before April 2010 and the measurement made at the initial evaluation in patients diagnosed with GEP-NETs after April 2010. A paired CgA test was defined as two consecutive plasma CgA determinations in patients at the beginning and end of tumor response evaluation. Our Institute was the only central laboratory to provide CgA measurement for such patients in Taiwan. Plasma CgA level was measured using a commercial kit (Chromoa assay; CIS Bio International). The chromoa assay is based on a sandwich enzyme-linked immunosorbent assay and uses two monoclonal antibodies that are directed against the central domain of the CgA molecule (amino acids 145-245). Each plasma sample was assayed duplicate and the mean optical density (OD) calculated. The OD values measured are proportional to the CgA protein concentration contained in the calibrators and samples. The reportable range was 7 ng/ml to 5,000ug/ml. The interassay coefficient of variation (CV) for CgA was <9% and the intra-assay CV was <5%. An elevated CgA level was defined as a level above the cut-off value of 94 ng/ml on the basis of our previous report (20).

*Calculation of percentage changes in paired CgA tests (ΔCgA) and tumor response*. The percentage change in ΔCgA was calculated as: (CgA level at the beginning of the tumor response evaluation – CgA level at the end of the tumor response evaluation)×100%/CgA level at the beginning. Tumor response was evaluated by imaging studies according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (22). This study investigated the predictive value of ΔCgA in patients receiving systemic antitumor therapy; therefore, CgA levels used were those for which the patient received a concurrent imaging scan within one week of CgA measurement. Paired CgA tests that were normal at both the beginning and the end of the response evaluation, and patients with unmeasurable disease were excluded from the calculations. Thirty-eight patients with a total of 116 ΔCgA measurements with concurrent imaging studies (CT or MRI) separated by intervals of 2-6 months (the exact interval was at the physician's discretion) were available for this study.

*Statistical analysis*. The patients' demographic data were summarized as the number (%) for categorical variables, and the median and range or interquartile range (IQR) for continuous variables. The frequency of elevation of the baseline CgA level >1-fold the UNL was tabulated as the number (%) and compared with respect to the clinical variables examined using the $\chi^2$ test or Fisher's exact test if the number in any cell was less than 5. Overall survival times were calculated from the date of the baseline CgA measurement to the date of the patient's death, or the end of the study period. Survival time was calculated using the Kaplan–Meier method, and all comparisons used a two-sided log-rank test. Multivariate Cox's proportional hazard model analysis was performed to investigate the impact of independent factors (sex, age, performance status, primary tumor localization, functional status, WHO tumor grade, numbers of organs with metastases and baseline CgA level) on overall survival. The ΔCgA was compared between subgroups using the Mann–Whitney test, and any significant difference between subgroups was further analyzed *post hoc* using

Dunn's test. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were calculated to determine the optimal ΔCgA cut-off value for predicting tumor response and accuracy. SPSS for Windows statistics software version 17.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. A *p*-value less than 0.05 was considered indicative of statistical significance.

## Results

Table I shows the patients' demographic data and tumor characteristics. The median age of the patients was 56.5 years, and 55% were female. Most patients (77%) had good performance status with the Eastern Cooperative Oncology Group (ECOG) performance scale scores of 0 or 1. The three most common primary tumor locations were the pancreas (32 patients, 53%), unknown primary (12 patients, 20%) and small bowel (6 patients, 10%). The tumors were functional in 21 out of 60 patients (35%). The distribution of patients with each tumor grade was nearly uniform. Metastasis had occurred in one organ in 26 patients (43.3%) and at least two organs in 34 patients (56.7%). The liver was the most common (86.7%) site of metastasis, followed by lymph nodes (35%), peritoneum (15%) and bones (15%).

A total of 52 out of the 60 patients (86.7%) had an elevated baseline plasma CgA level (>94 ng/ml). The frequency of elevation of plasma CgA level at baseline did not differ significantly with respect to age, gender, ECOG performance scale status, tumor functional status, tumor grade, the number of organs affected by metastasis, presence of hypertension, elevated liver function, renal insufficiency, or therapy with proton pump inhibitor or somatostatin analog. Patients with primary tumors in the rectosigmoid had a significantly lower rate (40%) of elevated baseline plasma CgA relative to patients with other primary tumor locations ($p$=0.019).

As of the end of October 2013, the median duration of follow-up was 11.2 (range=0.7-42.2) months and 30 at of 60 patients (50%) remained alive. Table II summarizes the prognostic factors of overall survival in our 60 patients with GEP-NETs. Survival differed significantly between patients with ECOG performance scale scores of 0-1 *versus* scores of 2-3 ($p$<0.001), pancreatic *versus* non-pancreatic primary tumor location ($p$=0.008), functional *versus* non-functional tumor ($p$=0.027), metastasis to one *versus* more than one organ ($p$=0.001), and baseline CgA level less *versus* more than 2-fold over the UNL ($p$=0.02). After multivariate analysis, only ECOG status [0-1 *versus* 2-3: hazard ratio (HR)=0.30; 95% confidence interval (CI)=0.10-0.91; $p$=0.034], tumor grade (1 *versus* 3: HR=0.03, 95% CI=0.005-0.17; $p$<0.001; 2 *versus* 3: HR=0.06,95% CI=0.014-0.25; $p$<0.001), number of organs affected by metastasis (1 *versus* >1: HR=0.20,95% CI=0.07-0.60; $p$=0.004) and baseline CgA level (less *versus* more than 2-fold over the UNL: HR=0.06; 95% CI=0.01-0.25; $p$<0.001) were independent prognostic factors. The cumulative overall

Table I. *Patients' demographic data, tumor characteristics, and frequency of elevation of baseline plasma chromogranin A (CgA) level.*

| Item | n (%) | Elevation of baseline CgA level, n (%) | *p*-Value |
|---|---|---|---|
| All patients | | 60 (100) | 52 (86.7) |
| Gender | | | |
| Male | 27 (45) | 24 (88.9) | 0.47 |
| Female | 33 (55) | 28 (80) | |
| Median age (IQR), years | 56.5 (45.8-68.3) | | |
| ≤55 | 31 (51.7) | 27 (87.1) | 1 |
| >55 | 29 (48.3) | 25 (86.2) | |
| ECOG performance | | | |
| 0 | 13 (21.7) | 12 (92.3) | 0.61 |
| 1 | 33 (55) | 28 (84.8) | |
| 2 | 5 (8.3) | 5 (100) | |
| 3 | 9 (15) | 7 (77.8) | |
| Tumor location | | | |
| Pancreas | 32 (53.3) | 30 (93.8) | 0.019 |
| Stomach | 5 (8.3) | 5 (100) | |
| Small bowel | 6 (10) | 5 (83.3) | |
| Rectosigmoid | 5 (8.3) | 2 (40) | |
| Unknown | 12 (20) | 10 (83.3) | |
| Functional tumor | | | |
| No | 39 (65) | 32 (82.1) | 0.16 |
| Yes | 21 (35) | 20 (95.2) | |
| Functional tumor type | | | |
| Gastrinoma | 8 (13.3) | 8 (100) | -- |
| VIPoma | 8 (13.3) | 7 (87.5) | |
| Insulinoma | 1 (1.7) | 1 (100) | |
| Carcinoid | 3 (5) | 3 (100) | |
| Glucagonoma | 1 (1.7) | 1 (100) | |
| WHO tumor grade | | | |
| 1 | 21 (35) | 19 (90.5) | 0.49 |
| 2 | 19 (31.7) | 15 (78.9) | |
| 3 | 20 (33.3) | 18 (90) | |
| No. of organs affected by metastasis | | | |
| 1 | 26 (43.3) | 22 (84.6) | 0.72 |
| >1 | 34 (56.7) | 30 (88.2) | |
| Organ affected by metastasis | | | |
| Liver | 52 (86.7) | | -- |
| Bone | 9 (15) | | |
| Lung | 6 (10) | | |
| Peritoneum | 9 (15) | | |
| Lymph nodes | (35) | | |
| Presence of hypertension | | | |
| Yes | 7 (11.7) | 6 (85.7) | 0.94 |
| No | 53 (88.3) | 46 (86.8) | |
| Elevated AST level > 1×UNL | | | |
| Yes | 17 (28.3) | 16 (94.1) | 0.27 |
| No | 43 (71.7) | 36 (83.7) | |
| PPI therapy | | | |
| Yes | 13 (21.7) | 11 (84.6) | 0.56 |
| No | 47 (73.8) | 41 (87.2) | |
| Baseline somatostatin analog therapy | | | |
| Yes | 11 (18.3) | 10 (90.9) | 0.54 |
| No | 49 (81.7) | 42 (85.7) | |
| Renal insufficiency | | | |
| Yes | 3 (5) | 3 (100) | 0.65 |
| No | 57 (95) | 49 (86) | |

ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; AST, aspartate aminotransferase; UNL, upper normal level; PPI, proton pump inhibitor; VIPoma: neuroendocrine tumor that produce vasoactive intestinal peptide.

Table II. *Prognostic factors of overall survival of patients with gastroenteropancreatic neuroendocrine tumors.*

| Factor | n (%) | Univariate *p*-Value | Multivariate *p*-Value | Adjusted hazard ratio (95% CI) |
|---|---|---|---|---|
| Gender | | | | |
| Male | 27 (45) | 0.08 | 0.73 | |
| Female | 33 (55) | | | |
| Age, years | | | | |
| ≤55 | 31 (51.6) | 0.11 | 0.13 | |
| >55 | 29 (48.4) | | | |
| ECOG performance score | | | | |
| 0-1 | 46 (76.7) | <0.001 | 0.034 | 0.30 (0.10-0.91) |
| 2-3 | 14 (23.3) | | | 1 |
| Primary tumor location | | | | |
| Pancreas | 32 (53.3) | 0.008 | 0.28 | |
| Other | 28 (46.7) | | | |
| Functional tumor | | | | |
| No | 21 (35) | 0.027 | 0.53 | |
| Yes | 39 (65) | | | |
| WHO grade | | | | |
| 1 | 21 (35) | <0.001 | <0.001 | 0.03 (0.005-0.17) |
| 2 | 19 (31.7) | | <0.001 | 0.06 (0.014-0.25) |
| 3 | 20 (33.3) | | | 1 |
| No. of organs affected by metastasis | | | | |
| 1 | 26 (43.3) | 0.001 | 0.004 | 0.20 (0.07-0.60) |
| >1 | 34 (56.7) | | | 1 |
| Baseline CgA level | | | | |
| <2 × UNL | 24 (40) | 0.02 | <0.001 | 0.06 (0.01-0.25) |
| >2 × UNL | 36 (60) | | | 1 |

CI, Confidence interval; ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; CgA, chromogranin A; UNL, upper normal level.

survival curves of patients stratified by variables significant in the multivariate analysis are presented in Figure 1.

Thirty-eight patients with a total of 116 ΔCgA (median, two paired tests per patient; range=1-9) between the beginning and end of tumor response evaluation were analyzed for correlation with patient's tumor response. Treatment strategies corresponded to the 116 ΔCgA in 38 patients are presented in Table III. Long-acting somatostatin analog-based therapy constituted the most common treatment strategy (54%), followed by targeted-therapy with either sunitinib or everolimus (26%), cytotoxic chemotherapy (10%) and surveillance (9%).

Distributions of ΔCgA with respect to tumor response are presented in Table IV. Median ΔCgA were −45.2% (range=−92.2 to 27.7%), −9.9% (range=−96.8 to 199.7%), and 77.1% (range=−2.5 to 1645.3%) for partial response (PR), stable disease (SD) and PD, respectively. ΔCgA differed between the PR and SD ($p$=0.008), PR and PD ($p$<0.001), and the SD and PD ($p$<0.001) groups (Figure 2). ΔCgA differed significantly between PR or SD and PD ($p$<0.001) regardless of whether the treatment was somatostatin-based therapy or not.

Figure 3 shows the ROC curve and AUC of the predictive value of the ΔCgA for tumor response. A valueg ΔCgA >17% in patients with GEP-NET distinguished PR and SD from PD with 91.2% sensitivity and 82.9% specificity (c-statistic 0.93; 95% CI=0.89-0.98).

## Discussion

Our findings identified that ECOG performance scale, WHO tumor grade, number of organs affected by metastasis, and baseline plasma CgA levels were independent prognostic factors in patients with GEP-NETs. The baseline plasma CgA was elevated in 87% of our patients with advanced GEP-NETs and was a valuable predictor of clinical outcome. ΔCgA calculated from the percent change in consecutive plasma CgA measurements of patients at the beginning and end of tumor response evaluation was helpful for assessing the response to treatment. To the best of our knowledge, our study is the first to address the prognostic and predictive value of plasma CgA in an Asian population of patients with GEP-NET.

The ESMO guidelines recommend measurement of plasma CgA levels during diagnosis, treatment, and follow-up in patients with GEP-NET (19). However, the National Comprehensive Cancer Network (NCCN) guidelines disagree on measurement of plasma CgA in patients with

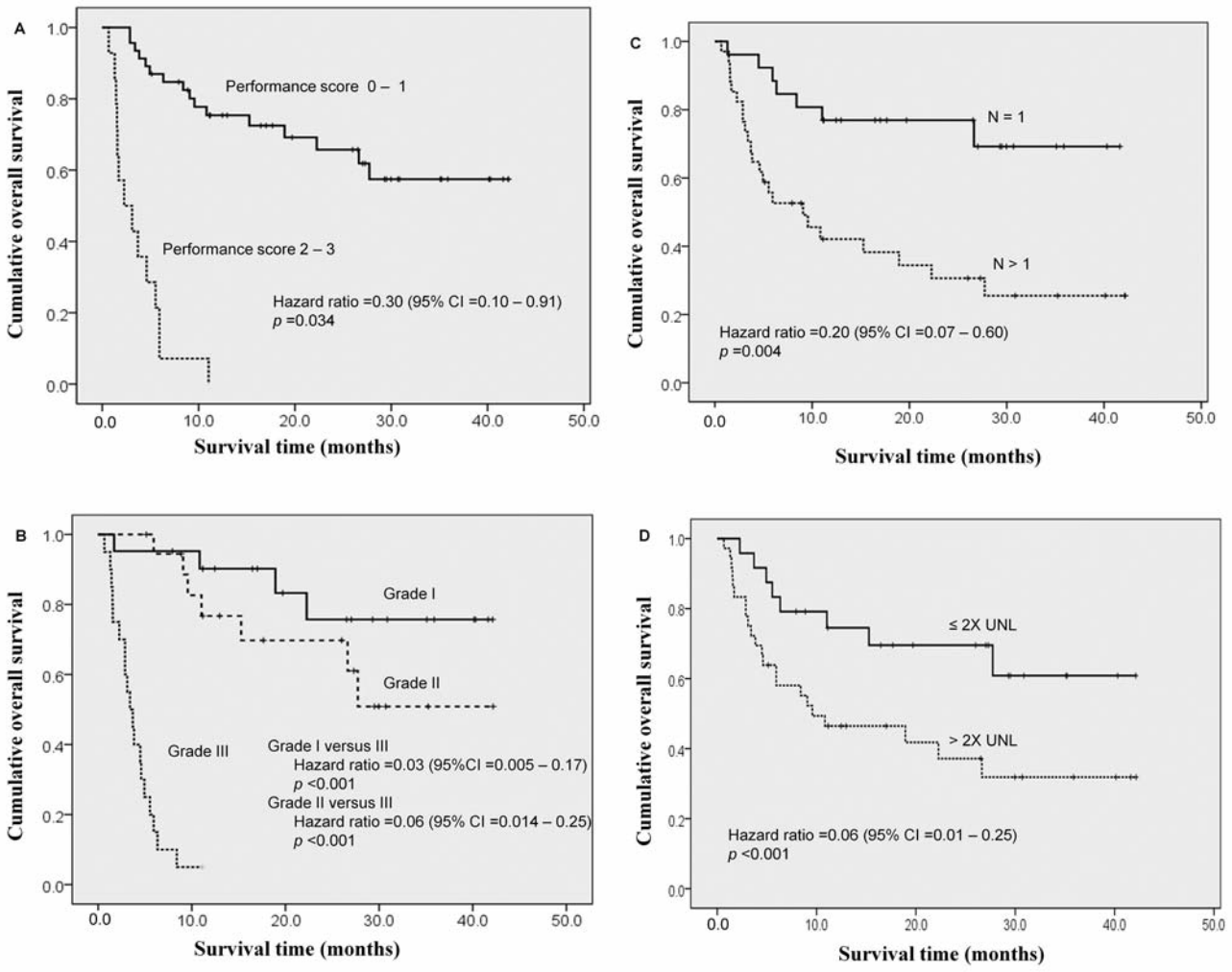


Figure 1. *Overall survival of patients with gastroenteropancreatic neuroendocrine tumors stratified by Eastern Cooperative Oncology Group performance score (A), tumor grade (World Health Organization, 2010) (B), number of organs affected by metastasis (C) and baseline plasma chromogranin A level (D). CI, Confidence interval; UNL, upper normal level.*

NET (23). One of the reasons for this disagreement is the frequency with which an elevated level of plasma CgA produces a false-positive diagnosis of NET. Plasma CgA levels may be elevated in patients who have non-NET malignancies, hepatic impairment, or renal insufficiency, or who are being treated with proton pump inhibitors (24, 25). An elevated plasma CgA level must be interpreted with caution in patients with the above conditions. Another reason is the rate of false-negative results produced by plasma CgA level in patients with NET: depending on the tumor status and measurement technique, 20-40% of patients with NETs do not exhibit an elevated CgA level (2-7, 11). Elevation of plasma CgA level in patients with GEP-NET has been shown to be associated with tumor burden (6), tumor functional status (3, 18), level of tumor differentiation (4, 18), and location of the primary tumor (3). Our study found that plasma CgA is a biomarker of GEP-NET frequently present in Asian populations, and the frequency of elevated plasma CgA at baseline in patients with GEP-NET did not differ with respect to tumor differentiation, number of organs affected by metastasis, or tumor functional status. Patients with primary tumors in the rectosigmoid had a significantly lower frequency of elevated plasma CgA than those with other primary sites; this result was consistent with previous studies that reported weak CgA expression by immunohistochemical staining in hindgut NET tissue (26, 27). Because of the relatively high rate of false-negative diagnosis of hindgut NET by plasma CgA level, testing for this biomarker is questionably useful in such patients and the results should be interpreted with caution.

Table III. *Treatment strategies corresponding to the 116 measurements of percentage changes in paired CgA tests (ΔCgA) in 38 patients.*

| Treatment strategy | Number (%) of tests |
|---|---|
| Surveillance | 11 (9.4) |
| Everolimus or sunitinib | 30 (25.9) |
| Cytotoxic chemotherapy | 12 (10) |
| Long-acting somatostatin analog-based therapy | 63 (54.3) |
| Somatostatin-alone | 46 (39.7) |
| Combined with sunitinib or sunitinib | 14 (12) |
| Combined with cytotoxic chemotherapy | 3 (2.6) |
| Overall | 116 (100) |

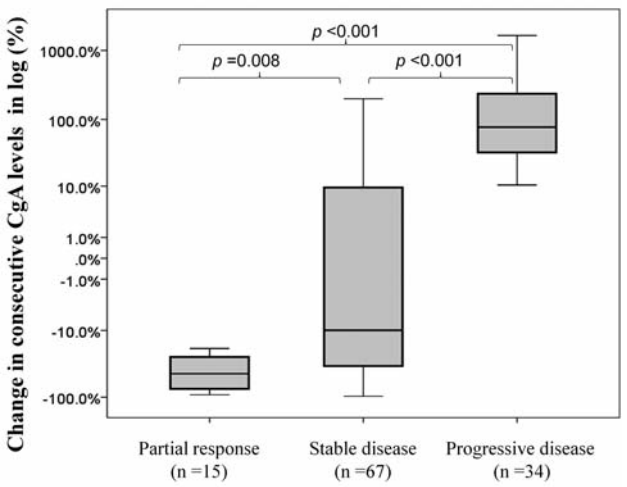


Figure 2. *Distribution of percentage changes in paired CgA tests (ΔCgA) with respect to the tumor response.*

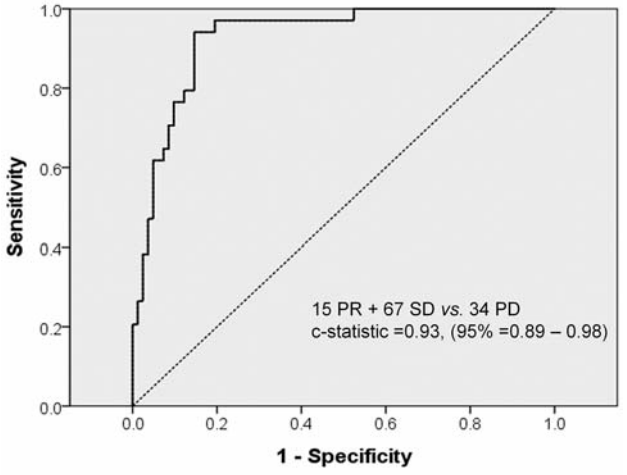


Figure 3. *Receiver operating characteristic (ROC) curves of percentage changes in paired CgA tests (ΔCgA) with respect to tumor response: partial response (PR, n=15) and stable disease (SD, n=67) versus progressive disease (PD, n=34). CI, Confidence interval.*

Baseline plasma CgA level is associated with tumor burden and patient outcome (13-17). However, the optimal cut-off value of baseline plasma CgA for predicting patient outcome remains uncertain. A plasma CgA cut-off value of one-fold over the UNL failed to exhibit prognostic value (18), possibly because elevation of plasma CgA is frequent among patients with advanced/metastatic GEP-NET (87% in this study) and because the CgA level can be slightly elevated in other conditions (24). Yao *et al.* used a cut-off value of two-fold over the UNL to predict outcome in order to avoid interference from mild elevation of plasma CgA level caused by other, benign conditions (15). Patients with higher baseline plasma CgA levels may have worse outcomes, as for patients with levels >5,000 u/L in the report of Janson *et al.* (13); however, using a higher value of baseline plasma CgA as the cut-off point (such as 5- or 10-times the UNL) did not provide better discrimination of prognosis in our interim analysis (data not shown). In line with Yao *et al.'s* finding (15), our study showed that a baseline plasma CgA level of twice the UNL was an independent prognostic factor in patients with GEP-NET.

Bajetta *et al.* reported that the plasma CgA levels increased in 83% of patients with NET with disease progression and in 100% of patients with progressive liver metastases (11). Serial plasma CgA values reported by Nehar *et al.* showed 80% concordance between changes in series CgA levels of over 25% and tumor progression (6). By the same definition as Nehar *et al.,* the concordance between ΔCgA and tumor progression was 88% (30/34) in our study.

Yao *et al.* reported that patients with early plasma CgA responses who received everolimus treatment experienced longer progression-free survival and overall survival than those without it (15). The plasma CgA levels measured 3 and 6 h after acute somatostatin administration had decreased significantly from baseline according to Massironi *et al.* (18); furthermore, they found that a decrease of baseline plasma CgA levels shortly after acute somatostatin administration of >30% predicted subsequent tumor response, long-term plasma CgA response, symptomatic response, and overall survival in patients with GEP-NET who were receiving long-term somatostatin treatment. Therefore, plasma CgA response is a potential predictor of treatment outcome in patients with pancreatic NET treated with everolimus, or in those with GEP-NET treated with a somatostatin analog. Similar to their observations, our previous report revealed that a decrease in

Table IV. *Analysis of the distribution of percentage changes in paired CgA tests (ΔCgA) with respect to tumor response stratified by treatment strategy.*

| Treatment strategy | Tumor response | n (%) | ΔCgA (%), median (range) | *p*-Value |
|---|---|---|---|---|
| Overall | PR | 15 (12.9) | −45.2 (−92.2 to 27.7) | *vs*. SD=0.008 |
| | SD | 67 (57.8) | −9.9 (−96.8 to 199.7) | *vs*. PD=0.001 |
| | PD | 34 (29.3) | 77.1 (−2.5 to 1645.3) | *vs*. PR=0.001 |
| Somatostatin-based therapy | PR | 5 (7.9) | −31.4 (−91.8 to 25.0) | *vs*. SD=0.31 |
| | SD | 40 (63.5) | −20.2 (−96.9 to 93.3) | *vs*. PD=0.001 |
| | PD | 18 (28.6) | 100.9 (−2.5 to 1645.3) | *vs*. PR=0.001 |
| Non-somatostatin therapy | PR | 10 (18.9) | −46.5 (−92.2 to 27.7) | *vs*. SD=0.003 |
| | SD | 27 (50.9) | −1.9 (−76.2 to 199.6) | *vs*. PD=0.001 |
| | PD | 16 (30.2) | 77.1 (10.4 to 450.3) | *vs*. PR=0.001 |

PR, Partial response; SD, stable disease; PD, progressive disease.

plasma CgA level from baseline of 20% or more suggested a PR or SD (20). The present study expanded our previous finding and confirmed that ΔCgA is helpful for predicting treatment response. In the present study, ΔCgA was significantly greater in patients with progressive GEP-NET than those with PR or SD, and a cut-off value of 17% exhibited 91.2% sensitivity and 82.9% specificity for predicting PD. The ability of ΔCgA to distinguish PR and SD from PD was similar in patients receiving somatostatin-based therapy and those not. ΔCgA had predictive value as a complement to imaging studies in patients receiving antitumor therapy. Calculation of ΔCgA might assist clinicians in adjusting treatment strategies before the results of imaging studies are available.

The NCCN practice guidelines recommend surveillance with imaging every 3-12 months for patients with asymptomatic GEP-NET or low tumor burden because of the wide variation in tumor behavior (23). Two recent phase III randomized studies showed that administration of either sunitinib or everolimus improved progression-free survival *versus* placebo among patients with well-differentiated pancreatic NETs in whom tumor progression was documented within 12 months prior to the start of the study (28, 29). Our study recommends close monitoring of plasma CgA level in regular follow-up of patients, as a sharp increase in ΔCgA of >17% during surveillance probably indicates tumor progression and warrants an early imaging study and intervention to achieve a better clinical outcome.

This study had several limitations. Firstly, this was a retrospective study of the clinical utility of plasma CgA level in patients with GEP-NET at a single medical center and included a patient group heterogeneous with respect to primary tumor location and anti-tumor treatment. Secondly, this study used ΔCgA in order to avoid confounding from the variable time intervals between consecutive plasma CgA measurements among our patients. Because the timing of consecutive plasma CgA measurements was not planned in advance, we were unable to address the prognostic value of the percentage change in plasma CgA level over a given interval with respect to treatment modality, as was done for pancreatic NETs treated with everolimus. Thirdly, because of the wide variation in treatment strategies, which included surveillance, a long-acting somatostatin analog, targeted-therapy, chemotherapy, and combination therapy, no detailed analysis of the rate of change in plasma CgA levels with respect to individual treatment strategies was possible. Finally, we did not adjust for patient characteristics (such as administration of proton pump inhibitors or the severity of liver impairment) that may influence plasma CgA level. Therefore, our findings may not be representative of all patients with GEP-NET. A prospective study is required to evaluate the prognostic and predictive values of the plasma CgA levels in Asian patients with GEP-NET.

## Conclusion

Our study showed that the baseline plasma CgA levels predicted overall survival and ΔCgA predicted treatment response in Asian patients with GEP-NET. Plasma CgA levels should be obtained at baseline and during treatment to predict overall survival and to guide treatment plans.

## Conflicts of Interest

The Authors declare that they have no competing interests. This study was financially supported by Novartis (Taiwan) Co., Ltd., in the form of the chromogranin A test kits.

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