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Increased gastric fluid DNA: a possible biomarker for gastric cancer diagnosis, prognosis, and disease progression

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Introduction

Gastric cancer is one of the most common cancer types. Given the importance of early detection of this type of cancer, investigations have been conducted to reveal new biomarkers capable of improving diagnosis, prognosis and to monitor disease progression as well as recurrence after treatment. Liquid biopsies have been proven to be very powerful tools, mainly based on the detection and analysis of cell-free DNA found in the plasma. Our group pioneered the study of the DNA content of gastric fluids and has been vetting the utility of its tumor-derived DNA cargo. Here we investigated the clinical applications of a quantitative analysis of DNA-content in the gastric fluid (gf) of subjects that underwent upper endoscopic evaluations.

Patients, Materials and Methods

All subjects studied here have been examined by upper digestive endoscopy at the A.C.Camargo Cancer Center, São Paulo, Brazil (ACC; IRB-protocol 2134/15). We evaluated 1056 patient-derived gastric fluid samples. After excluding cases with conditions such as partial or total gastrectomy, esophagectomy, portal hypertension, and other tumors, a total of 941 subjects remained. We evaluated the concentration gfDNA including subjects with normal gastric mucosa (n = 10), peptic diseases (n = 596), pre-neoplastic conditions (n = 99), and cancer (n = 236). gfDNA amounts were investigated according to DNA origin (host x microbiota), age of the subjects, gender, BMI, gastric fluid pH, use of proton-pump inhibitors, tumor subtypes & histological grades, clinical stages, and disease progression. Baseline gfDNA levels for patient groups were given as a median. Analyses were performed in the RStudio, using Mann-Whitney and Kruskal-Wallis tests for comparisons among two and three groups respectively.

Results

In the non-cancer group we observed that gfDNA levels are increased in women as compared to men ($p=7.44e^{-4}$), however this gender difference disappears for those with cancer (Figure 1). gfDNA levels are also increased in tumor versus non-tumor gastric fluid samples ($p=3.612e^{-12}$), in tumor versus normal and peptic diseases (5.672e-13), in tumor versus pre-neoplastic disease ($p=1.529e^{-06}$) (Figure 2) and more advanced tumors (T3) as compared to early stages (T2 and below) ($p=5.97e^{-4}$) (Figure 3). Moreover, our results suggested that patients with lower levels of gfDNA (≤ 1.28 ng/μL) had an increased risk of neoplastic disease progression during 3 years (p = 0.009) (Figure 4). Besides, whereas gfDNA showed an AUC comparable to some frequently used cancer antigens (0.658) it is likely its major utility would be related to the capability of revealing genomic alterations useful for gastric cancer monitoring.

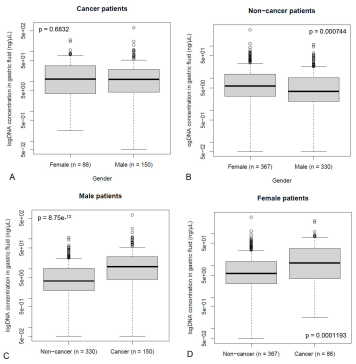


Figure 1 – gfDNA levels for males and females, with or without gastric cancer diagnosis. Females and males with (A) or without cancer (B). Males (C) or females (D) with or without cancer.

Results

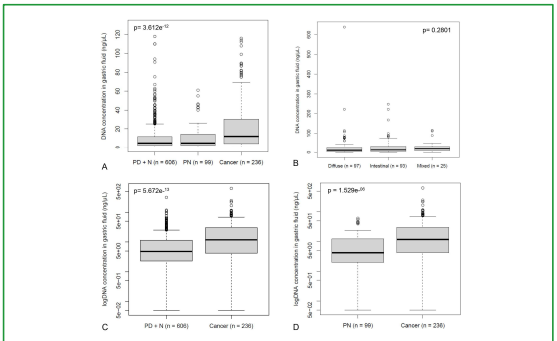


Figure 2 – A) gfDNA concentration (ng/μL) in patients with no findings after endoscopic examination (Normal, N) and the diagnosis of peptic diseases (PD), preneoplastic conditions (PN), and cancer. B) gfDNA concentration in patients diagnosed with diffuse cancer compared to intestinal and mixed cancer. C) A combination of the groups PD + N versus the cancer group. D) gfDNA concentration in gastric fluids (ng/μL) of patients with the preneoplastic conditions (PN) versus cancer diagnosis.

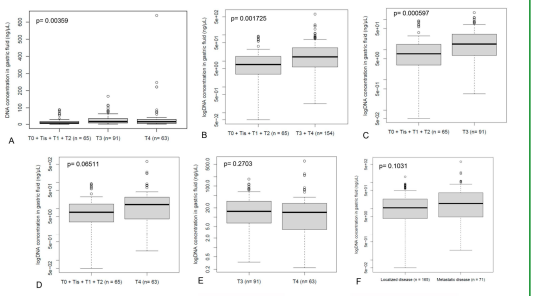


Figure 3 – A) gfDNA concentrations (ng/μL) in patients with early-stage disease (tumor stages 0, Tis, 1, and 2 (T0 + Tis + T1 + T2), as compared to T3 and T4 disease stage. B) gfDNA concentrations (ng/μL) in patients with early disease (tumor stages 0, Tis, 1, and 2 (T0 + Tis + T1 + T2) as compared to T3 plus T4 disease stage. C) gfDNA concentrations (ng/μL) in patients with early disease (tumor stages 0, Tis, 1, and 2 (T0 + Tis + T1 + T2) as compared to T3 disease stage. D) gfDNA concentrations (ng/μL) in patients with early disease (tumor stages 0, Tis, 1, and 2 (T0 + Tis + T1 + T2) as compared to subjects with the more advanced disease stage (T4). E) gfDNA concentrations (ng/μL) comparison between T3 versus T4 disease stages. F) gfDNA concentrations (ng/μL) comparison between localized and metastatic disease.

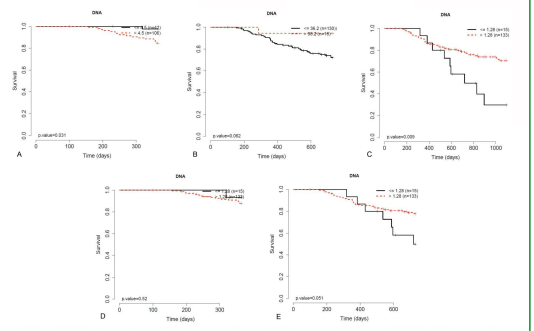
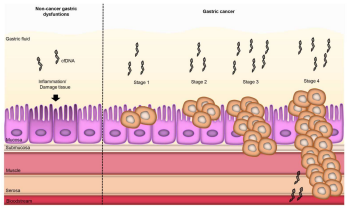


Figure 4 – Correlations between gfDNA levels relate with patients survival (Figure 4A - C) and survival free of tumor progression (Figure 4D - E). We followed up 148 (non-metastatic) cancer patients for a mean time of 3 years. Survival times were censored in 3 years and an algorithm was used to search for the cutoff on DNA concentrations that would split the patients in groups, according to the logrank test (Figure 4A - C). We fixed the cutoff value for DNA concentrations (1.28 ng/μL) and the logrank tests were repeated with survival times censored in 1 and 2 years (Figure 4D – E).

Conclusions

This is the first study to demonstrate the value of gfDNA quantification as a possible gastric cancer biomarker, focusing on cancer detection, prognosis, and disease progression. Taking this into account, we hope that our study will encourage the collection and study of gastric fluids, a source of potentially rich and informative biomarkers of the gastric environment that may facilitate the comprehension of gastric diseases.



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