Role of chromogranin A-derived fragments after resection of non-functioning pancreatic neuroendocrine tumors

Valentina Andreasi[1,2,3,5˚], Stefano Partelli[1,2,3˚], Marco F. Manzoni[3,4], Francesca Muffatti[1,3], Luigi Di Filippo[3,4], Stefano Crippa[1,2,3], Angelo Corti[2,3,5], Massimo Falconi[1,2,3*]

[1]*Pancreatic Surgery Unit, Pancreas Translational & Clinical Research Center, IRCCS San Raffaele Scientific Institute, Milan, Italy*

[2]*Vita-Salute San Raffaele University, Milan, Italy*

[3]*San Raffaele Hospital Neuroendocrine Tumor Group (ENETS Center of Excellence)*

[4]*Endocrinology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy*

[5]*Tumor Biology and Vascular Targeting Unit, Experimental Oncology Division, IRCCS San Raffaele Scientific Institute, Milan, Italy*

Introduction: No single reliable biomarker is available for non-functioning pancreatic neuroendocrine tumors (NF-PanNETs). Vasostatin-1 (VS-1), the N-terminal fragment of chromogranin A (CgA), seems to be a more accurate biomarker compared to its precursor[1,2].

Aim: The primary aim of this study was to investigate the ability of VS-1, compared to total-CgA, to assess the effectiveness of surgical resection performed for NF-PanNETs. The secondary aim was to evaluate two additional CgA-derived fragments, pancreastatin (PST) and vasostatin-2 (VS-2), as possible biomarkers for NF-PanNETs.

Methods: Consecutive patients who underwent surgery for sporadic NF-PanNETs at San Raffaele Scientific Institute (2018-2019) were included (n = 35). Plasma levels of CgA and CgA-derived fragments were measured by Enzyme-Linked ImmunoSorbent Assay (ELISA), preoperatively and postoperatively.

Results: Preoperative VS-1 was significantly higher compared to VS-1 measured on postoperative day 5 (POD 5) (pre: 0.338 nM *versus* POD5: 0.147 nM, $p < 0.001$), whereas total-CgA plasma levels significantly increased after surgery (pre: 1.123 nM *versus* POD5: 1.949 nM, $p = 0.006$). Overall, 24 patients showed at least 1 feature of tumor aggressiveness (i.e. T3-T4, nodal/distant metastases, Ki67 >5%, microvascular/perineural invasion, necrosis). The median percentage decrease in VS-1 plasma levels was 63% (IQR 28-88%) among patients with aggressive tumors, compared to 13% (IQR 0-57%) in the remaining population ($p = 0.033$). No significant differences in terms of PST ($p = 0.870$) and VS-2 ($p = 0.909$) plasma levels were observed between preoperative and postoperative time.

Conclusions: VS-1 provides an early assessment of surgical efficacy in patients who undergo resection for NF-PanNETs, especially in those with aggressive neoplasms. Total-CgA, PST and VS-2 have no clinical utility in this setting.

References

1. Corsello, A. et al. Vasostatin-1: A novel circulating biomarker for ileal and pancreatic neuroendocrine neoplasms. PLoS One 13, e0196858 (2018).
2. Andreasi, V. et al. Association between preoperative Vasostatin-1 and pathological features of aggressiveness in localized nonfunctioning pancreatic neuroendocrine tumors (NF-PanNET). Pancreatology 19, 57–63 (2019).