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Topic: Neuroendocrine Tumors

Circulating neuroendocrine tumors biomarkers. Why? When? How? Suggestions for clinical practice from guidelines and consensus

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ABSTRACT

Neuroendocrine neoplasms (NETs) are rare tumors that are increasing in incidence. NETs are characterized by heterogeneous biological behaviour, clinical presentation and course. A sensitive and specific diagnostic and prognostic circulating biomarker useful for all sites, grading and staging of neuroendocrine tumors is still an unmet need. The aim of this article was to review current neuroendocrine and oncologic scientific society guidelines and position statements, and propose recommendations for the most frequent clinical practice queries on circulating neuroendocrine tumors biomarkers. The authors searched for NCCN, NANETS, ESMO, ENETS, UKINETS, AME management guidelines or position statements available from PubMed up to 7th January 2016. From these results we chose guidelines or position statements published by scientific societies or institutions in USA, Europe and Italy with recognized expertise in neuroendocrine tumor patient management. The authors present suggestions for clinical practice based on this analysis.

Key words: Neuroendocrine tumors; neuroendocrine markers; neuroendocrine management; chromogranin A; guidelines; clinical practice

INTRODUCTION

Neuroendocrine tumors (NETs) are rare but have been increasing in incidence.[1] NETs are characterized by heterogeneous biological behavior, clinical presentation, and course. NETs arise from neuroendocrine cells aggregate in classical endocrine glands -- like adrenal, pituitary and parathyroid -- but also in the diffuse neuroendocrine system (DNES).

An early diagnosis is crucial since lower survival was demonstrated in patients with metastatic disease.[2] However an interval of many years is reported from earliest symptoms to diagnosis. Symptoms are often nonspecific and do not lend themselves to identifying the specific underlying tumor. In addition, clinical presentations are protean and mimic a variety of other non-neoplastic diseases.[3] Many specialists may be individually involved from earliest signs and symptoms but a multidisciplinary team may be the most successsful approach to reduce time latency from symptoms to diagnosis and improve overall survival.[4] In this context the choice of circulating neuroendocrine biomarkers and interpretation of these values needs to be carefully considered with respect to the clinical presentation and other putative diagnoses.[5,6] Many different diagnostic and therapeutic approaches are reported in real life NET manage-ment according to different physician expertise, accessibility of medical care in different countries, and financial reimbursement. Translation of guidelines and consensus into clinical practice is often difficult because suggestions are not always universally applicable.

The aim of our paper was to review current neuroendocrine and oncologic scientific society guidelines and position statements and provide recommendations for the most frequent clinical practice queries on circulating neuroendocrine tumor biomarkers.

We searched the National Comprehensive Cancer Network (NCCN), North American Neuroendocrine Tumor (NANETS), European Society of Medical Oncology (ESMO), European Neuroendocrine Tumor Society

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Table 1: Comparative practical clinical suggestion for circulating NET biomarkers use in functioning and non-functioning tumors from NCCN 2.2015, NANETS 2010-2013, ESMO 2012, ENETS 2009-2015-2016, UKINETS 2012 guidelines and AME posizione statement 2014

Source of indications	Cromogranin A	NSE	u-5HIAA	Plasma gastrin, insulin, glucagon, somatostatin, VIP, PP	Others (plasma calcitonin, GHRH, IGF1, ACTH, PTH-rp)*
NCCN 2. 2015[32]	YES for NENs diagnosis and FU		YES for diagnosis and FU	YES* for diagnosis and FU YES PP in pNEN for diagnosis and FU	YES* for diagnosis and FU
NANENS 2010-2013[29,37-40]	YES GEP-NENs diagnosis and FU (only if + at diagnosis and not resected) SUGGESTED THY-BRO NENs diagnosis and FU	Useful in THY-BRO diagnosis and FU	YES diagnosis and FU mid-gut NENs YES* others NENs	SUGGESTED** for diagnosis and FU (only if significant before)	SUGGESTED** for diagnosis and FU (only if significant before)
ESMO 2012[41-42]	YES GEP NEN diagnosis and FU YES THY-BRO diagnosis and FU	YES in THY-BRO	YES in SI-NEN YES* in THY-BRO	YES* for diagnosis and FU NF-pNEN USEFUL PP	YES* in THY-BRO (ACTH-GHRH-IGF1)
ENETS 2015-2016[11,22,25,31,43,44]	YES GEP-NEN diagnosis and FU USEFUL in NEC diagnosis and FU YES THY-BRO diagnosis and FU	Useful in NEC diagnosis and FU	YES in SI-NEN YES* in THY-BRO	YES* for diagnosis and FU	YES* for diagnosis and FU
UKINETS 2012[33]	YES for NENs diagnosis and FU		YES in SI, digiunal, colon, appendiceal NENs	YES* for diagnosis and FU NF-pNEN USEFUL PP	YES* for diagnosis and FU
AME 2014[5]	YES for GEP-NEN diagnosis and follow only after diagnosis or strong clinical suspicion		YES* diagnosis YES for FU if significant before	YES* NOT PP in pratical clinical use	YES*

NCCN: National Comprehensive Cancer Network; NANETS: North American Neuroendocrine Tumor; ESMO: European Society of Medical Oncology; ENETS: European Neuroendocrine Tumor Society; UKI NETS: UK and Ireland Neuroendocrine Tumour Society; NSE: plasmatic neuron-specific enolase; u-5HIAA: urinary 5-Hydroxy-indolacetic acid; NENs: neuroendocrine tumors; VIP: vasoactive ntestinal peptide; PP: pancreatic polypeptide; GHRH: growth hormone releasing hormone; IGF1: insulin like growth factor 1; ACTH: adrenocorticotropin; PTH-rp: parathyroid-hormone like hormone; YES: recommended; FU: follow up; YES*: recommended when clinically indicated; THY-BRO: neuroendocrine thymic and bronchial tumors; GEP-NEN: neuroendocrine gastroenteric tumors; SUGGESTED**: suggested a large panel of markers at diagnosis or key point individually tailored; NEC: neuroendocrine carcinoma; SI-NEN: small intestine neuroendocrine tumors; NF-pNENs: non functioning pancreatic neuroendocrine tumors; NOT: recommend against

relationship between biomarker level and the degree of disease burden, higher levels are frequent in patients with metastasis, particularly in the liver. In other words, circulating biomarkers may reflect the tumor burden. Circulating markers are useful for monitoring specific tumors by providing a surrogate endpoint: CgA for the majority of cases, pancreastatin for hepatic tumor load, and neurokinin A for serotonin-secreting tumors of the small bowel.[33] In particular, circulating CgA is higher in patients with large metastases compared with localized disease or even limited hepatic involvement (when assessed as < 25%, 25-50%, > 50%) and correlates with survival. In addition, CgA levels are reduced after hepatic resection or transplantation. In a retrospective study, a CgA decrease of 80% or more was predictive of complete symptom resolution and disease stabilization. By contrast, reduction of urinary 5-hydroxyindoleacetic acid concentrations of 80% or more (or normalization) was predictive of symptomatic relief but not of disease stabilization.[45]

Despite the fact that gastrinomas show high circulating

Table 2: Pitfalls and bottlenecks and possible remedies for circulating chromogranin A and gastrin interpretation

Pitfalls and bottleneck	Possible causes	Remidies suggested
High CrA levels during diagnostic work up for NETs	Others disease and cancers than NETs	Keep in mind non-malignant pathological causes of elevated CrA as severe hypertension, systemic inflammatory response syndrome, pulmonary obstructive disease, bowel disease renal insufficiency, liver or heart failure, chronic gastritis, chronic hepatitis, pancreatitis, Helicobacter Pylori infection, inflammatory bowel disease, hyperthyroidism, giant cell arthritis, systemic lupus erythematosous, exercise-induced physical stress
	Doubtful in accuracy determination	Keep in mind malignant pathological causes of elevated CrA others than NETs as breast cancer, hepatocellular carcinoma, pancreatic adenocarcinoma, colon cancer, ovarian cancer, prostate cancer, medullary thyroid cancer
	High individual intervariability	Recommend only certificated laboratories with high quality control certification
	Drugs (PPIs)	Complete with imaging according to clinical presentation Repeat determination if doubtful Stop proton pump inhibitor 2 weeks before or according with drugs half life
Unexpected individual changes in patient with known NETs	Doubtful in accuracy determination	
	High individual intervariability	Recommend only certificated laboratories with high quality control certification and the same laboratory and assay for each patient
	Different assay and normal values in different labs	Report information on lab and normal reference in patient medical record Check for possible new drugs or physiological interference (fasting, exercise *etc*.)
	Samples from different physiological condition	
	Consider drugs interference (SSA)	Recommend CrA determination during long acting SSA therapy at regular interval after drug injection If crucial data for diagnosis or therapy management retest in same condition Compare biochemical, clinical and imaging data
High gastrin levels in patient with clinical suspicion of gastrinoma	Drugs interference (PPIs)	Stop PPIs under careful patient monitoring (in-patient setting or daily checks) and switch to H2 receptor antagonist If PPIs interruption is not clinically indicated try to tapered the IPPs dose If the diagnosis is unclear (fasting serum gastrin < 10× increased, gastric pH < 2, no tumor imaged), a secretin test is indicated
	Concomitant disease interference	Consider atrophic gastric, Helicobacter Pylori infection, renal failure, short bowel syndrome

NETs: neuroendocrine tumors; PPIs: proton pump inhibitors; SSA: somatostatin analogues

CgA values even in the absence of liver metastasis, gastrin levels are generally proportional to tumor burden and highest gastrin levels are present in patients with metastatic disease. In addition, gastrin seems higher in pancreatic compared to duodenal primary tumors, with no discernible difference between sporadic and multiple endocrine neoplasia (MEN1) or Zollinger Ellison syndrome patients.[46] On the contrary, authors of a recent consensus agreed that circulating biomarkers levels in patients with neuroendocrine tumors do not correlate with tumor grade and do not differentiate low-level malignancy from high-grade disease.[12]

SHOULD CIRCULATING BIOMARKERS BE USED IN DISEASE FOLLOW UP?

When specific circulating biomarkers are elevated at the diagnosis in a patient there is indication to follow these over time. If new signs and symptoms emerge, it is necessary to test for new paraneoplastic syndromes according to clinical presentation.[6]

All guidelines [Table 1] recommend the use of CgA for follow up in all NETs even though there is an absence of prospective studies supporting its use.

SHOULD BIOMARKERS REFLECT INTERVENTION?

CgA has been used in gastroenteric NETs as a predictive biomarker to identify patients most likely to have durable responses to long acting somatostatin analogue therapy.[47] Further, early decreases in CgA after somatostatin analogues plus everolimus was predictive of early response in pNET patients.[34] Increases in CgA levels after radical surgery in a large Italian observational study was reported to be predictive of tumor relapse 9-12 months before the clinical and radiological evidence of disease recurrence.[48] In a recent paper, CgA was an early predictor of recurrence 6 months before radiological progression in metastatic NETs.[49] A reduction of > 80% in CgA after cytoreductive surgery was shown to predict disease control[50] and reduction of CgA was observed after successful peptide receptor radionuclide therapy[51] and liver transplantation.[52]

Table 3: Pitfalls and bottlenecks and possible remedies for circulating u-5HIAA

Pitfalls and bottleneck	Possible causes	Remidies suggested
High u-5HIAA in patient with suspected or known NETs	Urinary collection not correct	Give some written information how to collect 24 h urine and to conserve. If result is doubtful and crucial for diagnostic and therapeutic choose repeat
	Intraindividual Variation	Perform two consecutive 24-h urine collections and take mean value of these two especially when collection required for diagnosis or when crucial for terapeutic choose
	Doubtful in accuracy determination	Recommend only certificated laboratories with high quality control certification
	Others disease	Keep in mind others pathological causes of elevated u-5HIAA as coeliac and Whipple's disease, intestinal stasis and cystic fibrosis
	Tryptophan/ serotonin-riche food consumption	Exclude from the diet from 72 h preceding and during urine collection plums, pineapples, bananas, eggplants, tomatoes, avocados, walnuts, avocados, kiwi, pecans, coffee, tea, cocoa, chocolate, vanilla, sweets and cookies
	Drugs interference	Keep in mind possible drugs interference. Stop if not contraindicated. u-5HIAA levels were increased during Acetaminophene, naproxen, coumaric acid, phenacetin, diazepam, ephedrine, glyceryl guaiacolate, methocarbamol, reserpine, cisplatin, fluorouracil, melphalan, rauwolfia
		Give some written instruction on drugs and food restriction and report all drugs in medical records
Low u-5HIAA in patients with known or highly suspected NETs	Urinary collection not correct	The same as for high levels
	Intraindividual variation	Keep in mind possible drugs interference. Stop if not contraindicated. U-5HIAA levels were reduced during Chlorpromazine, heparin, imipramine, isoniazid, levodopa, monoamine oxidase inhibitors, methenamine, methyldopa, phenothiazines, promethazine, tricyclic antidepressants, chlorophenylalanine, corticotrophin, guanfacine, imipramine, isocarboxazid, isoniazid, levodopa, MAO inhibitors, moclobemide, acetylsalicylic acid, streptozotocina uses
	Doubtful in accuracy determination	
	Drugs interference	Ethanol reduce u-5HIAA
	Alcohol addiction	SSA is known to decrease u-5HIAA. Assays for diagnostic purposes should be made in patients not on somatostatin analogues therapy
	Possible inhibitory roles of SSA	In the follow up setting urinary samples need to be collected on stable or comparable SSA doses
		Report in patient medical record type of somatostatin analogue and frequency of administration and eventually subcutaneous octreotide performed in the last 24 h before determination

NETs: neuroendocrine tumors; PPIs: proton pump inhibitors; SSA: somatostatin analogues; u-5HIAA: urinary 5-Hydroxy-indolacetic acid

HOW TO AVOID MISINTERPRETATION OF CGA, GASTRIN AND U-5HIAA IN CLINICAL PRACTICE?

There are many conditions that interfere with CgA and u-5HIAA measurements. For CgA there is no universally accepted CgA assay and the different methodologies can lead to confusing results. Many physiological conditions as stress, pregnancy or exercise can increase circulating CgA levels and the same is true for many drugs and non-neuroendocrine diseases. U-5HIAA measurements also have inherent pitfalls since they require a 24 h urine collection and are subject to interference by dietary habits.[2,5,8,9,13-15,29,31,33] Tables 2 and 3 show the most important pitfalls and bottlenecks and possible remedies in CgA, gastrin and u-5HIAA interpretation and provide suggestions to reduce interference in circulating biomarker measurements for more accurate tumor management.

MONOANALYTE OR MULTIANALYTES?

The identification of effective biomarkers in patients with NETs is a high priority. In a recent Delphi consensus, the panel of neuroendocrine experts agreed that an acceptable standard for a diagnostic biomarker should have a sensitivity of at least 80%, specificity of at least 90%, and positive and negative predictive values of each at 80% or more.[12] In addition, the biomarker should be able to provide information regarding the proliferative and metastatic capacity of a tumor, the identification of surgical and medical treatment effectiveness and correlate with patient survival. Unfortunately current universal circulating biomarkers are not able to provide this standard and, in particular, the role of CgA in the diagnosis of neuroendocrine tumors is decreasing.

The principal limitation in the measurement of circulating CgA is the absence of a gold standard assay and wide variability of results from different kits and laboratories. In addition, false positive results are reported as a result of other neoplasia (prostate and breast cancer and hepatocellular carcinoma) and common conditions (kidney, liver or heart failure, chronic gastritis, inflammatory bowel disease, PPI use, essential hypertension and physical stress). In addition, the current biomarkers used for gastroenteropancreatic NETs are inadequate for bronchopulmonary NETs and vice versa. For these reasons, a multianalyte approach would likely be more effective compared to a monoanalyte circulating biomarker. To this end, a specific multianalyte assay with algorithmic analyses (MAAA) named NETest has recently been developed. NETest is a PCR-based, 51-transcript signature that is based on correlating and normalizing multiple sets of variables that represent gene clusters specific to NETs and their biological behavior. The use of this blood-based test is proposed to facilitate early detection of disease recurrence and to predict therapeutic efficacy. The diagnostic performance of MAAAs was better when compared to CgA (93-98% *vs.* 50-80%)[53,54] exceeding the performance criteria proposed by an expert panel convened to evaluate NET biomarkers. MAAAs and NETest in particular may improve diagnostic accuracy and offer better interdisciplinary perspective than single analyte testing.

IS THERE A CLINICAL ROLE FOR NOVEL BIOMARKERS?

Recently, several novel biomarkers for NETs have been developed using an integration of genomics and technology platforms. In addition to gene transcript by MAAAs, circulating tumor cell (CTC) and microRNA (miRNA) analyses have been proposed.[12]

Khan *et al*.[55] showed that the number of CTC detected in patients with neuroendocrine tumors was comparable to other tumors in which CTC have been shown to have prognostic relevance. In this study, 47% of patients with midgut (n = 101) and 24% of patients with pancreatic (n = 42) tumors had ≥ two CTC detected. Presence of CTC was clearly associated with increasing tumor burden and weakly with tumor grade. In a more recent, large prospective study, the same group demonstrated that changes in CTC were associated with response to treatment and overall survival in metastatic neuroendocrine tumors, suggesting CTC may be useful as a surrogate marker to direct clinical decision making.[56] Although there is an increasing interest in CTC as a biomarker, recent consensus concluded that CTC analyses have several technical limitations and need further validation before being adopted into routine clinical practice.[12]

There is also increasing interest in miRNAs as clinical biomarkers of tumorigenesis, treatment response and outcomes, but to date clinical data are scarce and clinical application challenging. Similarly, there are several novel monoanalyte assays (i.e. connective tissue growth factor for carcinoid heart disease (CCN2) or paraneoplastic Ma antigen 2 (PNMA2) for small intestinal neuroendocrine tumors, but these analyses are not available in clinical practice.[12] Further, panelists of the recent Delphi consensus gave the strongest support to the use of emerging biomarkers in multianalyte technology based on genomics.[12]

CONCLUSION

To date, the identification of sensitive, specific and reproducible NET circulating biomarkers for the prediction, diagnosis, prognosis and classification of NETs and to evaluate changes during therapy has been limited[12] and remains an unfulfilled unmet medical need as defined by the 2007 National Cancer Institute NET meeting.[57] There are no specific circulating monoanalyte biomarkers for neuroendocrine tumors that fulfill the NIH recommended criteria and the search continues for

markers with diagnostic and prognostic capabilities. Since Feyrter have discovered the neuroendocrine equivalent of Pandora's Box, a unique relationship between these various neuroendocrine peptides and different tumors has not been found yet.[7] We are hopeful that in the era of Precision Medicine, specific circulating markers or a multianalyte panel for specific tumor types can be developed for NETs giving more reliable diagnostic and prognostic information. The road is long and new, robust prospective studies in different neuroendocrine tumors settings are required before new accurate biomarkers are validated and implemented into routine clinical practice.

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