Neurokinin A is a sensitive circulating biomarker for neuroendocrine tumours of the midgut. Audit of 1000 consecutive raised NKA results in a routine regulatory peptide laboratory

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Introduction:

Neuroendocrine tumours of the mid gut are one of the more common NETs comprising more than one quarter of the total group. A significant number present early with acute bowel obstruction but the larger proportion present late with carcinoid syndrome and significant metastatic disease. Diagnosis is delayed because the presenting symptoms of intermittent abdominal pain, diarrhoea and flushing are more often reported by patients with more common diseases. By the time many of these patients are finally diagnosed with carcinoid many years may have elapsed form first symptoms, centres report 4-8years. Also the progression of this disease is from small tumour in the bowel to lymphatic and hepatic metastases while the primary tumour may remain very small, often too small to be visualized by radiology. Invariably the first indication of disease by imaging, is of liver infiltration.

Tumours of the mid gut may be indolent for decades but in other cases they may be aggressive form the start. The earliest possible diagnosis, therefore is important and as treatment options increase even with extensive secondary disease many patients survive with an excellent quality of life for many years. Because of the rarity of this disease screening is not an option.

Chromogranin A (CgA) is the only general marker for NETs but is not specific for any particular group of NETs and not specific for tumours of the midgut. In addition CgA is raised in other common situations, including autoimmune atrophic gastritis and during treatment with proton pump inhibitory drugs. As a result a large proportion of the specimens received by this laboratory show a raised CgA although only 5-10 % are from NET patients.

Midgut NETs secrete serotonin, but because of the difficulty in measuring setrotonin in the circulation the breakdown product, 5 hydroxy indole acetic acid (5HIAA) is measured by preference, in urine. This is a laborious and unpopular test and requires careful dietary restrictions for the days preceding .

The tachykinins are also secreted by tumours of the midgut, both substance P and NKA. We have measured both, but NKA has been a more reliable test and we have used this in the diagnosis of midgut NETs since 1986. We have previously published data from a retrospective study of 150 patients with midgut NETs and have shown NKA to be the most sensitive laboratory test compared to CgA and urinary 5HIAA. A summary of these results are shown, following.

Figure 1
Circulating CgA concentrations (U/l) and extent of metastatic disease
CgA is a positive predictor of liver metastases p<0.0001...

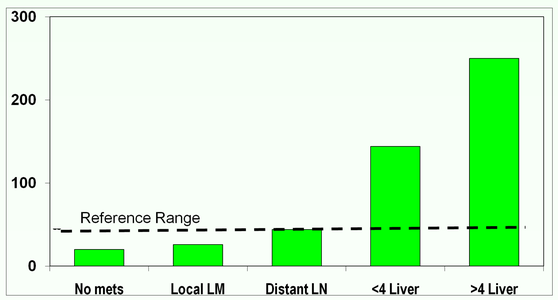


Figure 2
Urinary 5HIAA concentrations (umol/24h) and extent of metastatic disease
Urinary 5 HIAA is a positive predictor of liver metastases

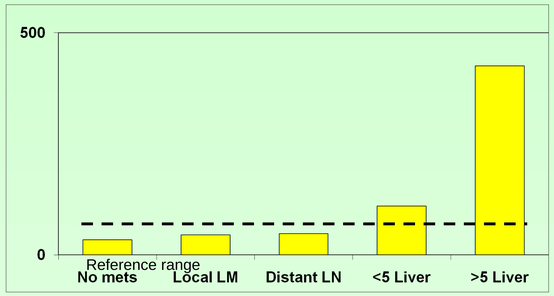
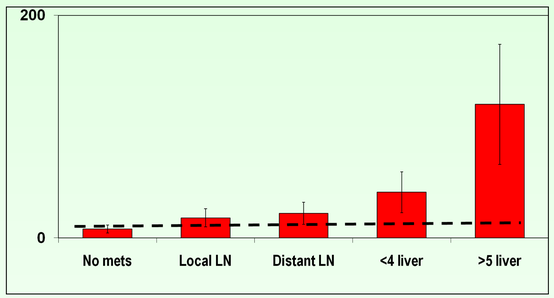


Figure 3
Circulating NKA concentrations (ng/l) and extent of metastatic spread
NKA is a positive predictor of metastatic disease including local lymph nodes P<0.001.



Methods

We have audited 1,000 consecutive specimens from patients in Northern Ireland, with raised NKA (Reference Range, RR <20ng/l.).
We recorded all CgA concentrations measured in the same specimen and urinary 5 HIAA when this test was performed within 4 weeks of the blood specimen. For all patients with one raised test pathology records were interrogated for tissue biopsy results on that patient.
We have a policy that for all NKA tests which are above the RR we request a repeat specimen. For tests reporting NKA >30ng/l (from patients not already on the NET specialist clinic list) we suggest that the patient be referred to that clinic for further investigation.
We have audited all repeat NKA requests and repeat 5HIAA as a result of the first laboratory report.

Results

Of the 1,000 specimens with raised NKA, 743 were from patients with confirmed midgut tumours. These corresponded to 124 individuals. The diagnosis associated with the 1000 specimens is shown (Table 1). The data have been updated from the abstract because of further follow up.
Urinary 5HIAA was tested in 316 specimens. Thirty eight from patients with tumours of the midgut recorded concentrations within the RR when NKA was elevated .

Table 1

NKA ng/L	TOTAL	MGC	Renal Or other NET	MGC Excluded	Under Study For MGC	Repeat NKA/ 5HIAA Normal	No Follow Up
>100	221	220	1	0	0	0	0
51-100	165	158	1	4	1	1	1
41-50	78	71	0	4	1	1	1
31-40	148	104	10	10	5	12	7
26-30	152	94	17	4	1	23	13
21-25	236	106	31	0	4	71	24

In 124 (40.8%) of the individuals recording NKA >RR the diagnosis of midgut tumour was confirmed. A further 32 individuals (10.5%) had other NETS. Of this group 2 were suspected of having a midgut tumour in addition to the other NET and 8 had advanced pancreatic NETs which were secreting a number of different biomarkers.
Five patients are under investigation and 6 were investigated extensively with no confirmation of a midgut tumour confirmed. Specificity for MGC is >90% when NKA is >30ng/l. Forty six individuals have not been followed up 9 with NKA >30ng/l, 3 deceased within 4 weeks of the test.

Table 2

Patient diagnosis	No. specimens	No. individuals	% of all individuals
Total	1000	304	
MGC	753	124	40.9
Renal Failure	6	4	1.3
Other NETs	53	32	10.5
Patient under further investigation for MGC	12	5	1.6
Patient studied MGC excluded	22	6	2.0
repeat NKA normal 5HIAA normal NKA and /or 5HIAA	72 62 110	87	28.6
No Follow up	46	46	15.1 3 (NKA>30ng/L)

Conclusions

1 NKA is an excellent biomarker for NETs of the midgut and is more sensitive than CgA and Urinary 5HIAA.

2 The range 21-30ng/l is indeterminate, and the test should be repeated.

3 The range >30ng/l has a specificity of >90% for MGC.

4 The range 21-30ng/l is important for detecting early recurrence in MGC.