A systematic review of diagnostic procedures to detect midgut neuroendocrine tumors
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CRD summary
This review compared diagnostic yield in tests for midgut neuroendocrine tumours. It concluded that urinary 5-hydroxy indole acetic acid level should be used in patients with flushing/persistent unexplained diarrhoea; abdominal CT scan and OctreoScan should be used for suspected neuroendocrine tumours. Yield estimates were varied within tests and the reported data are not sufficient to support the practice recommendations provided.

Authors' objectives
To assess the diagnostic yield of clinical procedures used to diagnose midgut neuroendocrine tumours.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews were searched (January 1998 to October 2007) for studies published in English, Dutch, Spanish, German, French, or Italian; search terms were reported. Bibliographies of included studies were screened for additional articles.

Study selection
Studies on the clinical presentation and/or preoperative diagnostic assessment of patients with suspected neuroendocrine tumours located in the midgut (duodenum, jejunum, ileum, appendix, or caecum) were eligible for inclusion. Studies were required to include at least 10 patients with suspected neuroendocrine tumours located in the midgut and had to report diagnostic yield, defined as the percentage of correctly diagnosed neuroendocrine tumours out of the total number of patients tested.

Most included studies were conducted in the USA; two studies were conducted in the UK. The pooled male to female ratio for participants in included studies was 0.81 (range 0 to 1.85); their mean or median age ranged from 32 to 63 years. Most neuroendocrine tumours were located in the small bowel (53.7%) or the appendix (32.9%). Nodal metastases were present at diagnosis in 11.9% of study participants and nodal or liver metastases were present in 23.3%. Diagnostic tests evaluated included endoscopy, endoscopic ultrasound, video-capsule endoscopy, abdominal computed tomography (CT), abdominal magnetic resonance imaging, contrast radiography, $^{131}$-meta-iodobenzylguanidine (MIBG) scintigraphy, urinary 5-hydroxy indole acetic acid (5-HIAA) level and chromogranin serum levels.

Two reviewers independently assessed studies for inclusion; any disagreements were resolved by consensus.

Assessment of study quality
The methodological quality of the articles was independently assessed by two reviewers. Quality criteria were based on the Cochrane Handbook for Systematic Reviews of Interventions (observational studies) and included: number of patients taking part in the study (greater or fewer than 30 patients); tumour site was clearly indicated (yes or no); clear description of the patient pathway from symptom presentation to diagnosis (yes or no); comparison of the diagnostic tools utilised (yes or no); and prospective or consecutive study with a clear description of the molecular diagnosis. An overall quality score (maximum 7) was determined for each study.

Data extraction
The numbers of patients undergoing each diagnostic procedure assessed and the numbers of neuroendocrine tumours detected by each procedure were extracted.

Data were also extracted on the symptoms of patients with midgut neuroendocrine tumours (not included in this abstract).

The authors did not state how many reviewers performed the data extraction.
Methods of synthesis
Pooled estimates of diagnostic yield were calculated for each diagnostic test and ranges were also reported; the method used to derive pooled estimates was not specified. The Yates corrected $\chi^2$ test was used to compare pooled diagnostic yields, with $p<0.05$ considered as significant.

Results of the review
Seventeen studies (n=7,464 participants) were included in the review. The number of participants diagnosed with neuroendocrine tumours ranged from 11 to 92 per study. The overall quality scores of included studies ranged from 2 to 4 points, with most studies (nine) scoring 2 points. Most studies (15) were retrospective, and most (13) did not use the specified method to determine final diagnosis.

The diagnostic yields for all midgut neuroendocrine tumours were: 78.9% (range 20 to 100; three studies) for angiography; 56% (range 0 to 100; five studies) for endoscopy; 86.6% (range 0 to 100; seven studies) for CT; 60% (one study) for video-capsule enteroscopy; 90.5% (range 65 to 100; three studies) for OctreoScan; 59.1% (range 43 to 66; two studies) for $^{131}$I-MIBG scintigraphy; 51.6% (range 5 to 100; four studies) for contrast intestinal radiography; 17.9% (range 0 to 20; three studies) for chromogranin serum level; and 37.5% (range 0 to 100; 10 studies) for 5-HIAA urinary level.

The pooled diagnostic yields of endoscopy, intestinal contrast radiology, and video capsule endoscopy were similar. The pooled diagnostic yields of CT and angiography were also similar. The pooled diagnostic yield of OctreoScan was significantly higher than that of $^{131}$I-MIBG scintigraphy ($p<0.001$). The pooled diagnostic yield of urine 5-HIAA level was significantly higher than that of serum chromogranin A ($p=0.001$). Data were also reported separately for neuroendocrine tumours of the duodenum, jejunum/ileum, and appendix.

The authors presented a diagram showing a possible algorithm for the diagnostic work-up of midgut neuroendocrine tumours.

Authors' conclusions
Urinary 5-hydroxy indole acetic acid level was the first test to apply in patients with flushing or persistent, unexplained diarrhoea. Abdominal CT scan and OctreoScan should be used whenever neuroendocrine tumour is suspected.

CRD commentary
The review provided a clearly stated objective and defined inclusion criteria. A number of sources were searched for relevant studies and, although some language restrictions were applied, the inclusion of six European languages may have limited the potential for language bias. Unpublished data were excluded, which left open the possibility of publication bias. Reported search dates were inconsistent between the abstract and the main text. Methods to minimise error and/or bias were applied to study selection and quality assessment, but it was unclear whether similar measures were applied to the data extraction process.

The use of pooled estimates of diagnostic yield was not informative as considerable heterogeneity between studies was apparent. Diagnostic yield data are of limited value in determining the most appropriate diagnostic pathways as they provide no information on the numbers of erroneous test results that may be expected. Additionally, the studies included in this review reported heterogeneous estimates of yield within diagnostic tests.

The data reported are not sufficient to support the authors' conclusions/recommendations for practice.

Implications of the review for practice and research
Practice: The authors stated that urinary 5-HIAA should be the preferred test for patients presenting with flushing or persistent, unexplained diarrhoea. Patients with upper gastrointestinal symptoms should undergo endoscopy, and double-contrast small bowel radiography should be used in patients presenting with bowel obstruction. Video-capsule enteroscopy should be used when there is occult gastrointestinal bleeding. Abdominal CT scan followed by OctreoScan should be used where neuroendocrine tumour is suspected.
Research: The authors did not specify any recommendations for future research.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.