Carcinoembryonic antigen (serum)

1 Name and description of analyte

1.1 Name of analyte
Carcinoembryonic antigen (CEA)

1.2 Alternative names
None

1.3 NMLC code

1.4 Description of analyte
CEA is a glycoprotein of MW approx. 180 kD found in normal fetal gastrointestinal tissue; it is normally present at only very low concentrations in adult plasma but its concentration is increased in the presence of many tumours, particularly colorectal cancers (70%). Increased concentrations have also been described in gastric, bronchial, uterine and ovarian cancers, and in lymphomas.

1.5 Function of analyte.
The normal function of CEA is unknown.

2 Sample requirements and precautions

2.1 Medium in which measured
CEA is measured in serum.

2.2 Precautions re sampling, handling etc.
General precautions only.

3 Summary of clinical uses and limitations of measurements

3.1 Use
CEA is recommended for use only to monitor possible recurrence in some patients following resection of colorectal cancer. It is not recommended as a diagnostic test.

3.2 Limitations
1. CEA is insufficiently sensitive or specific to be of value in screening for or diagnosing colorectal cancer.
2. CEA has been used extensively for monitoring tumours other than colorectal but is not recommended for this purpose and in many instances superior markers are now available.

4 Analytical considerations

4.1 Analytical method
CEA is measured by immunoassay.

4.2 Reference method
None reported.

4.3 Reference materials: The WHO Expert Committee on Biological Standardisation has established the preparation coded 73/601 (National Institute for Biological Standards and Control, USA) as the 1st International Reference Preparation of CEA.

4.4 Interference
As with all immunometric assays, there is a potential for interference by *in vivo* heterophilic antibodies. Results must always be considered in relation to the clinical situation and to previous assay results, if available. The latter is particularly important when serial results are being used for monitoring the response to treatment.

4.5 Sources of error
At very high concentrations, there is a risk of assays generating falsely low values as a result of the high dose hook effect.

5 Reference intervals and variance

5.1.1 Reference interval: the upper reference limit is ~2.5 µg/L
5.1.2 Reference intervals (others): the upper reference limit in smokers is ~5.0 µg/L
5.1.3 Extent of variation
5.1.3.1 Interindividual CV: this is not a useful concept with tumour markers
5.1.3.2 Intraindividual CV: 13%
5.1.3.3 CV of method: 5%
5.1.3.4 Critical difference: ~36%
5.1.4 Sources of variation
[CEA] is increased in smokers and in some patients with inflammatory bowel disease and chronic liver disease.

6 Clinical uses of measurement and interpretation of results

6.1 Uses and interpretation
CEA is only recommended for monitoring certain patients following resection of colorectal cancer. It should not be used for screening or diagnosis. A concentration >50 µg/L is effectively diagnostic of metastases being present.
The half-life in plasma is approximately 4.5 days. A longer apparent half-life following surgery suggests incomplete resection.

6.2 Confounding factors
1. The specificity of CEA (30–80%) for colorectal cancer is compromised by its plasma concentration not being consistently elevated in colorectal cancer: it may be undetectable or present at only low concentrations with poorly differentiated tumours.
2. The sensitivity of CEA (~40%) for colorectal cancer is compromised by its being detectable in some benign, conditions (particularly gastrointestinal) and in some non-colorectal tumours, e.g. gastric, cervical and non-small cell bronchial carcinomas.
3. Smokers frequently have higher plasma concentrations of CEA than non-smokers (typically up to twice the value).

7 Causes of abnormal results

7.1 High values

7.1.1 Causes

- High values are found in many, but not all, patients with colorectal carcinoma and less frequently in a variety of other tumours as well as occasionally in benign conditions. Since mmeasurement of CEA should not be used as a screening test (i.e. in the absence of clinical evidence of cancer) the action to be taken if an unexpectedly high [CEA] is found will not be considered here.
- A failure of an elevated [CEA] to fall following surgical resection of a tumour suggests either incomplete resection, local recurrence or the presence of hepatic metastases. [CEA] increases less frequently with metastases to the lungs.
- A rise in concentration of 1 μg/L following an initial fall after resection (even if the second result is below the upper reference limit) suggests recurrence or metastasis (sensitivity 80%, specificity 86%).

7.1.2 Investigation

If CEA is misused as a screening test for cancer and a high value is found, the appropriate further investigation will depend on any clinical findings. In an asymptomatic non-smoker, with only a slightly elevated value, a pragmatic approach would be to repeat the test after one month: a rising value would be more likely to represent malignancy than a stable one.

7.2 Low values

7.2.1 Causes

CEA should be undetectable or present in only very low concentrations in healthy individuals; the concept of a low value is not applicable.

7.3 Note

As with all tumour markers, a fall in concentration or the disappearance of CEA from the plasma may be due to a change in the tumour such that CEA is no longer expressed. This appears to be an unusual phenomenon with colorectal cancers.

8 Performance

8.1 Sensitivity, specificity etc: see 6.2 for colorectal cancer; values are lower for other tumours.

9 Systematic reviews and guidelines

9.1 Systematic reviews

None identified.

9.2 Guidelines

Published guidelines and recommendations are in broad agreement that CEA measurements should only be used as part of follow-up for attempted curative surgery in colorectal cancer (e.g. SIGN Guideline no 67: Management of Colorectal Cancer: March 2003 updated September 2011 http://www.sign.ac.uk/guidelines/fulltext/67/index.html). The evidence suggests that using CEA for this purpose allows detection of

recurrence or metastasis some six months earlier than if it is not used. There is, however, inconsistent evidence as to whether measuring CEA in this way affects clinical outcome.
Atkins CD. Guidelines for the use of carcinoembryonic antigen in colorectal cancer. Journal of Clinical Oncology 1997,15:863-864.
Scheer RA, Auer RA. Surveillance after curative surgery of colorectal cancer. Clinical Colonic and Rectal Surgery 2009;22:242-250 (*includes summary of current published guidelines*).

9.3 Recommendations

1. The American Society of Clinical Oncology recommends that CEA concentrations are measured at three monthly intervals for at least three years in patients with Dukes' stage B or C disease who would be candidates for liver resection, and to monitor metastatic disease during systemic treatment. It is not recommended for screening or as a guide to adjuvant treatment. (http://www.guidelines.gov/context.aspx?id=20014) accessed 20.i.2010.
2. These recommendations are supported in other documents, e.g.
a. Duffy MJ. Carcinoembryonic antigen as a marker for colorectal cancer: is it clinically useful? Clinical Chemistry 2001,47: 624-630.
b. Van Cutsem E, Dicato M Arber N *et al*. Molecular markers and biological targeted therapies in metastatic colorectal cancer: expert opinion and recommendations derived from the 11th ESMO/World Congress on Gastrointestinal Cancer, Barcelona, 2009. Ann Oncol 2010 Suppl 6:vi1-vi10.

10 Links

10.1 Related analytes: numerous tumour markers have been described but CEA has the best performance for colorectal cancer. Particularly for the newer markers, there is considerable overlap between the tumour types in which a given marker may be detectable, markers may be undetectable even in the presence of clinical disease (poor sensitivity) and their concentrations may be increased in benign conditions (poor specificity).

10.2 Related tests: see 6.3

10.3 Note

In the UK, there is a national screening programme for colorectal cancer based on the detection of stool occult blood with follow up of positive results using flexible colonoscopy.

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