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Friday, June 9, 2017

17:50 - 18:05 GP's Waste So Much Money on CEA

GPs waste a lot of money on CEA

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Rotorua GP CME 9/6/2017

MacMurray CENTRE
Digestive Diseases & Endoscopy

COUNTIES MANUKAU HEALTH

Outline

- Cases – Is CEA indicated?
- CEA – History and Background
- CEA – use in General Practice and Specialist Practice
- How often is it requested?
- Discussion and Recommendations

Case 1

- 47F Chinese self employed
- Asymptomatic – No gastro-intestinal symptoms
- Health check in China with various tumor markers including CEA
- CEA 5 on 3 occasions
- Should we investigate?

Case 2

- 33F Chinese
- Well
- Busy real estate agent
- No PMHx
- No FHx
- Minor upper gastrointestinal symptoms – dypepsia – OGD 12 months ago, normal, with normal biopsies (gastric, duodenal)
- Hb 95, ferritin 10 in the context of Menorrhagia

Labplus Test Guide

Carcinoembryonic antigen

Also known as : [CEA]

Plasma/Serum

Test performed by: LabPLUS Automation

Specimen Collection

4.5 mL PST Blood (Preferred)
0.5 mL Paediatric Micro-PST Blood (Preferred)
5 mL EDTA Blood
5 mL Heparin Blood
5 mL Plain Blood
3.5 mL SST Blood

Reference Intervals

Units: ug/L

Reference range: < 3.0 (non smokers)

Approximately 13% of otherwise healthy smokers have CEA levels of up to 5.0 ug/L

Uncertainty of Measurement: 16%

Turnaround Time: *Within 3 hours*

Diagnostic Use and Interpretation

This is a non-specific test which may be increased in both benign and malignant diseases.

It is therefore of limited use for diagnosis.

Its main value is for monitoring patients with tumours which secrete CEA. Levels fall with successful treatment and a rise may indicate tumour recurrence.

CEA may be elevated with the following carcinomas:

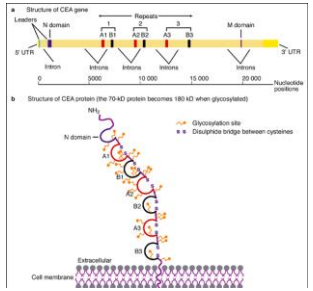
- Colorectal (70%)
- Pancreatic (55%)
- Gastric (50%)
- Lung (45%)
- Breast (40%)
- Uterine (40%)
- Ovarian (25%)

Benign conditions causing elevated CEA include:

- Cirrhosis (45%)
- Emphysema (30%)
- Rectal polyps (5%)
- Benign breast disease (15%)
- Ulcerative colitis (15%)

Carcinoembroyonic Antigen

- Described in 1965 by Gold and Freeman
- Present in fetal colon and colon adenocarcinoma (embryonic tissue and cancer)
- Absent from the healthy adult colon
- Subsequent studies found that CEA or a CEA-like molecule was also present in certain healthy tissues in lower concentrations
- Malignant tissue CEA 60-fold higher



Carcinoembryonic Antigen

- Initial study showed 35/36 with colorectal cancer had a high CEA – Thomson et al.
- High values not found in normals (pregnant women, non GI cancer, benign GI disease
- Results not validated, however CEA put into widespread use

Carcinoembyronic Antigen

- Significant heterogeneity – 60% carbohydrate (mannose, galactose, N-acteylglucosamine, fucose, sialic acid)
- Role in cancer dissemination – mice studies increased likelihood of liver metastasis
- Binds to certain strains of *Escherichia coli*

CEA and Colorectal Cancer

- Tumour Stage
  - Levels proportional to tumour stage
  - Eg Dukes A 28%, B 45% C 75% D 84% (CEA >2.5 hg/L)
  - If CEA >5 – A 3%, B 25%, C 45%, D65%
- Tumour Grade
  - Well-differentiated CRC produce more
  - Higher CRC grade not necessarily higher

CEA and Colorectal Cancer

- Tumour Site
  - Left sided tumours higher CEA
- Ploidy Status of Tumour
  - Aneuploid colorectal cancers produce higher concentations of CEA compared to diploid

CEA and Colorectal Cancer

- Screening
  - Using an upper limit of normal of 2.5ug/L
  - CEA sensitivity of 36% and specificity of 87% for screening for Duke's A and B CRC
  - In unselected populations prevalence of CRC is low – PPV therefore unacceptably low and is of little value in screening healthy subjects

CEA and Colorectal Cancer

- Diagnosis
  - Cut off of 2.5ug/L sensitivity ranges from 30-80% depending on disease stage
  - However, sensitivity in symptomatic patients is likely to be higher as they are more likely to have more advanced disease
  - Specificity – CEA is raised in both adenocarcinoma as well as benign diseases
  - Arguably if there are symptoms and CEA > 5 x ULN should be considered strongly suggestive of cancer

CEA and Colorectal Cancer

- Prognosis
  - Based on Duke's staging system
  - Importance for Dukes B to further prognosticate as 40-50% have aggressive disease and may benefit from adjuvant chemotherapy
  - High pre-operative CEA have worse outcome (5/7 studies)
  - But has it been proven that raised CEA Duke's B who receive chemo have a better outcome?
  - Post operative CEA should return to normal within 4-6 weeks – if not higher chance of recurrence

CEA and Colorectal Cancer

- Liver Metastasis
  - The liver in the main site for metastatic disease from CRC (60%)
  - 40% who die from CRC have metastases in the liver only
  - 25% of patients are amenable to hepatic resection with a 5 year survival of 21-48%
  - But 50-80% who undergo hepatic resection develop further recurrences
  - High pre-operative CEA and high post hepatectomy CEA 1-3 post op – adverse prognosis

CEA and Colorectal Cancer

- Post curative resection surveillance
  - Aim is to detect recurrent disease at and early and treatable stage
  - Studies in this area have been small and retrospective
  - However this seems to have a sensitivity of 80% (17-89%) and specificity of 70% (34-91%)
  - Heterogeneity of studies (frequency of testing and definition of raised CEA)
  - Most useful for detecting Liver Metastasis – sensitivity of 94%, specificity of 96% (one study 100% sensitivity)
  - Poor at detection of locoregional recurrence – however there has been a trial that shows superiority to endoscopy, CT and USS
  - Monitoring can detect recurrent CRC – lead time 5 months (4-10)
  - Cost-effective for the detection of potentially curable recurrent disease

CEA and CRC

- Recurrence
  - Sounds promising? Should all patients who undergo curative resection undergo CEA surveillance?
  - Ideally need large prospective RCT looking at Outcome, QoL, Cost
  - Meta-analysis 1998
    - Studies 1972-1996 – intensive follow up with serial CEA 3 x per year for 2 years, clinic visits vs symptomatic follow up in the control group
    - 2005 patients
    - Cumulative 5 years survival 1.16 x higher (p-0.003)
    - More than 2 x as many curative re-resections in the intensive group (p=0.0001)
    - Survival rate 3.6 x higher vs controls (p=0.0004)
    - Specific benefit of CEA NOT STUDIED
  - Further Meta-analysis yielded similar results

CEA for post operative recurrence

- **The diagnostic accuracy of a single CEA blood test in detecting colorectal cancer recurrence: Results from the FACS trial**
- 582 patients, 104 (17.9%) developed recurrence
- CEA > 5 – sensitivity 50% (95% CI: 40.1-59.9%)
- 56 missed recurrences (53.8%)
- 89 false alarms (56.7%) with 157 referred for further investigations – unnecessary investigations
- CEA >2.5 –missed recurrences 36.5%, false alarms 84% https://doi.org/10.1371/journal.pone.0171810 - March 2017

CEA and the Liver

- Liver Status
  - Liver is primary site for CEA metabolism
  - Certain benign liver diseases impair liver function and cause raised CEA

CEA and Bowel obstruction

- Bowel obstruction raises CEA
- Decompression reduces CEA

CEA and Smoking

- Study of 700 apparently healthy volunteers
- Male: Smokers 6.2 ug/L Non smokers 3.4 ug/L
- Female: Smokers 4.9ug/L Non smokers 2.5ug/L

CEA requested through Labtests - Auckland

- Labtests – sole community laboratory in Auckland
- 370 requests sent to Labplus per week
- Equates to 1500 per month
- 18000 per year
- CEA test costs $12.17 (Labplus) = $220k per year
- What is the cost of false positives in asymptomatic patients ?
- What is cost of false positives in detecting post operative recurrence?

Case 1

- 47F self employed
- Asymptomatic – No gastro-intestinal symptoms
- Health check in China with various tumor markers including CEA
- CEA 5 on 3 occasions
- Should we investigate?

Case 1 - Outcome

- Gastroscopy – Normal
- Colonoscopy – Ileitis – biopsies chronic inflammation – no granulomas, negative ASCA, ANCA
- Pillcam – Normal
- Undergoing a trial of 5ASA agent ? Early Crohn’s

Case 2

- 33F
- Well
- Busy real estate agent
- No PMHx
- No FHx
- Minor upper gastrointestinal symptoms – dypepsia – OGD 12 months ago, normal, with normal biopsies (gastric, duodenal)
- Hb 95, ferritin 10 in the context of Menorrhagia

Case 2 - Outcome

- Gastroscopy – normal with normal gastric and duodenal biopsies
- Colonoscopy – near obstructing tumour mid descending colon
- Staging CT – liver lesions ?benign
- CEA 3
- MRI – benign lesions
- For surgery – doing well

Summary and Conclusions

- CEA is not a perfect test
- CEA is not recommended as a screening test
  - False positives
  - Leads to unnecssary investigations and anxiety
- CEA is the best test for post-operative recurrence but is no where near perfect – does not replace endoscopy and CT scan
- What are the cost consquences of investigating false positives in the asymptomatic population remains to be answered
- If a patient has symptoms they require further investigations anyway – does CEA change management?

Questions?