CEA monitoring in colorectal carcinoma - to the limit of the guidelines and beyond

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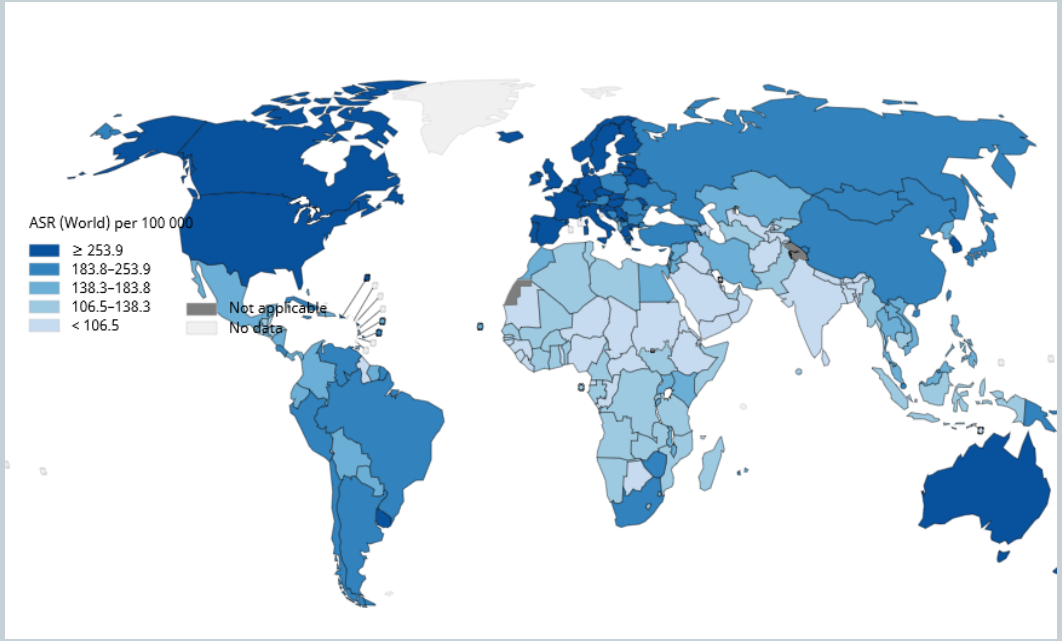
Compendium

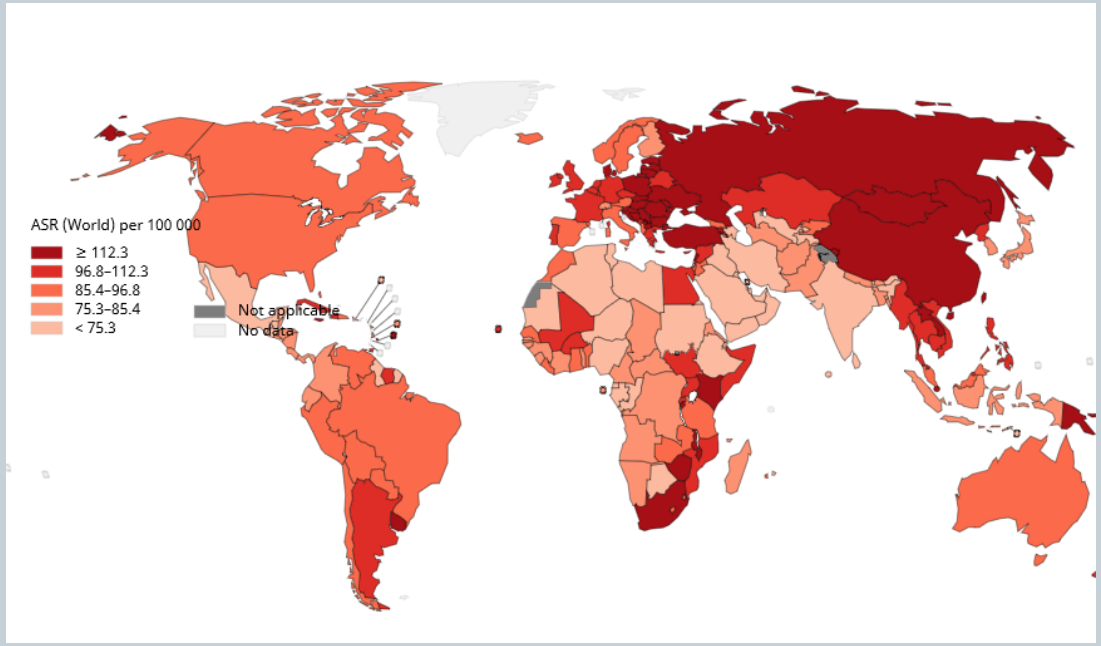
- INTRODUCTION
- HISTORY
- CEA IN COLORECTAL CARCINOMA MANAGEMENT- INDICATIONS
- ORIGINAL CASE REPORTS

CANCER EPIDEMIOLOGY

CANCER INCIDENCE

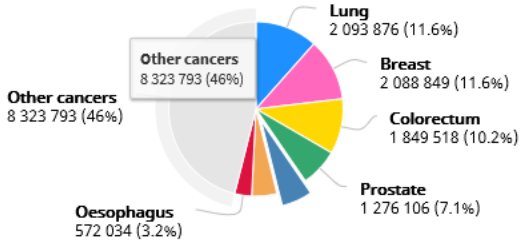


CANCER MORTALITY



CANCER EPIDEMIOLOGY- INCIDENCE

WHO



Total : 18 078 957

Data source:GLOBOCAN 2018
Graph production: Global Cancer Observatory (http://gco.iarc.fr/)
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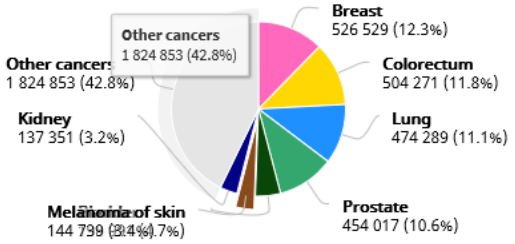
World Health Organization

BULGARIA



Total : 4 265 040

Data source:GLOBOCAN 2018
Graph production: Global Cancer Observatory (http://gco.iarc.fr/)
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HISTORY

- CEA was isolated in 1965 by Gold and Freedman as an oncofetal antigen, present in fetal gut, liver, and pancreas between 2 and 6 months of gestation. In the adult tissues it was demonstrated that identical antigens were present in all tested specimens of malignant tumors of the entodermally derived epithelium of the gastrointestinal tract and pancreas, but were absent from all other tested adult tissues. Nowadays it is considered that the carcinoembryonic antigens represent cellular constituents which are repressed during the course of differentiation of the normal digestive system epithelium and reappear in the corresponding malignant cells by a process of derepressive-dedifferentiation.

Gold P, Freedman SO. Specific carcinoembryonic antigens of the human digestive system. J Exp Med 1965;122(3):467-81

CEA in COLORECTAL MANAGEMENT

Carcinoembryonic antigen (CEA) is a well-established serum tumor marker in colorectal cancer management. It is used in:

- preoperative prognostication,
- disease stage prediction
- immediate post-resection assessment
- to some extend as an adjunct in treatment response monitoring.

The **diagnostic and screening** value of CEA is definitely **poor**, but the pre-operative determinations of the marker for **risk stratification** in patients with diagnosed colorectal cancer is widely **discussed** in the literature and is considered to be **recommended**.

CEA in COLORECTAL MANAGEMENT

- The discussion for the **preoperative testing** is much more connected with the clinical value of the marker, i. e. whether the patients with higher preoperative values to receive adjuvant therapy, due to the poorer prognosis, based on these higher values of CEA or not.
- The disease **stage prediction**, based on CEA is accepted and recommended by NCCN and ASCO, but it should be mentioned that the tumor marker values must **not be considered as an indication for adjuvant therapy**, but only for a basis for **intensive follow-up of patients in high risk** of recurrence.
- The data for the **immediate post-resection assessment** of CEA is under discussion and although there are some research studies that report positive results, the value of the marker is **not considered proven** and is not recommended in the official guidelines.

CEA in COLORECTAL MANAGEMENT

- The usage of the marker in the **recurrence monitoring** has a proven influence on the **survival** of patients with colorectal cancer. The major role of the marker, however, is in the monitoring/follow up of patients with colorectal cancer, treated with curative intent. **CEA value** in follow up of those patients is addressed in multiple randomized trials, meta analyses and systemic reviews, **reaching the highest evidence bases appraisal as a monitoring tool.**
- Although comparatively straight-forward, the diagnostic assessment in patients with elevated surveillance CEA levels may vary.
- Generally clinical examination, imaging (CT, MRI) and endoscopy (wherever applicable) should follow a confirmed CEA rise.

CEA in COLORECTAL MANAGEMENT

- There is a specific group of patients, where the so called conventional work up does not show a recurrence or fails to do so.
- In this scenario the clear clinical question is whether the increase in **CEA levels** is a **false positive** or a **true positive** data for recurrence.
- In those cases more sophisticated diagnostic work-up may be needed including **FDG PET CT and possibly novel biomarkers**.

CEA in COLORECTAL MANAGEMENT

- PET /CT shows high detection rate in previously not recognized colorectal cancer recurrence with rising CEA levels and is the modality of choice in this particular situation.
- If appropriately performed, it demonstrates detection rate as high as about 85% in rising CEA positive patients, which is in favor of predominantly malignant reasons.
- A CEA rise can also lead to detection of a synchronous/metachronous primaries that also produce high CEA levels. Here breast cancer, stomach and lung cancer, pancreatic cancer and mesothelioma should be mentioned.

CEA in COLORECTAL MANAGEMENT
ORIGINAL RESULTS

- Methods and criteria:
- 42 patients(22 ♀, 20 ♂, mean age 59.6 ± 9.2y), operated for colorectal carcinoma, rising CEA levels >3,5 µg/l during follow up, negative conventional imaging results.
- FDG PET /CT detected 34 true positive patients(81 %) and 8 false positive patients(19%).
- If CEA levels<10 µg/l PPV - 61%, CEA level over 10 µg/l – 96%, significant difference (p = 0.0037).

Y.Bocheva, Serum tumor markers in solid tumors, MU-Varna, 2016

CEA in COLORECTAL MANAGEMENT
ORIGINAL RESULTS

- Metastatic sites that may present as high CEA and could potentially be missed by conventional imaging are mostly lymph node metastases, peritoneal spread, local recurrence, liver and other rare locations.

Metastatic sites	Single	Multiple	Summary
Liver	5	9	14
Lymph nodes	4	12	16
Local recurrence	7	5	12
Lungs	1	5	6
Peritoneum	3	4	7
Others	0	5	5

Y.Bocheva, Serum tumor markers in solid tumors, MU-Varna, 2016

CEA in COLORECTAL MANAGEMENT

- The minority of patients with rising CEA levels may occasionally experience a recurrence despite negative results from the extensive work-up.
- Close CEA levels monitoring is essential in this scenario with the results going in two directions:
  - those with further rising CEA levels almost invariably recur
  - while those with high but stable CEA levels rarely experience recurrence.
  - The absolute CEA value is also important with serum levels of CEA of more than 10ng/ml being predictive of recurrence in very high proportion of patients.

Bocheva Y. Bochev P. Честота на рецидивите при пациенти с колоректален карцином и високи мониториращи нива на туморните маркери CEA и Ca 19-9, при които патологичният процес не се локализира с образни изследвания. Scripta Scientifica Medica, vol. 45, Suppl. 2, 2013, pp. 180-186

CEA in COLORECTAL MANAGEMENT

- However one should bear in mind that CEA levels rise in a variety of benign conditions and could reach excessive absolute values without a presence of malignancy.
- The most often and typical benign diseases, connected with CEA elevation are chronic hepatitis, cirrhosis, chronic kidney failure, colitis, jaundice.
- So neither the rise alone nor the absolute value but the trend of rising is predictive of recurrence if so-far work up has failed to localize disease.

CEA in COLORECTAL MANAGEMENT

- Even though guidelines and official recommendations are mostly clear about the role of CEA in the monitoring of colorectal cancer patients, treated with curative intent and the consecutive conventional and high-end imaging, the management of the patients with no recurrence detected is less clear.
- In these cases combined assessment with Ca 19-9 may be attempted, but with the clear idea that Ca 19-9 performs suboptimal in colorectal cancer and is a subject of broad spectrum of non-specificity.
- Another problem is that Ca19-9 and CEA may rise simultaneously in similar benign processes which limits the use of the combination of markers as differential diagnostic tool.

CEA in COLORECTAL MANAGEMENT

- In the present era of molecular and genetic testing attempts are made to correlate the rising monitoring CEA levels, such as circulating tumor cells, circulating free tumor DNA (cfDNA), methylated DNA (e.g septin 9), reporter mRNA etc.
- Attempts in this direction have been made also in the group of CEA positive FDG negative patients.
- None of the tests has however reached routine clinical use.

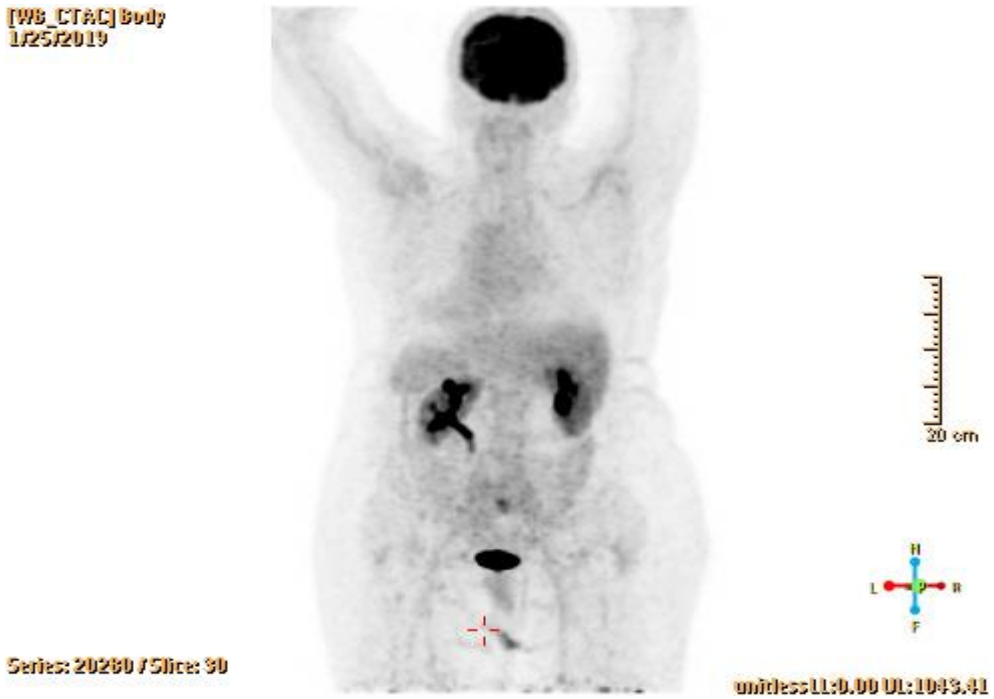
CEA in COLORECTAL MANAGEMENT

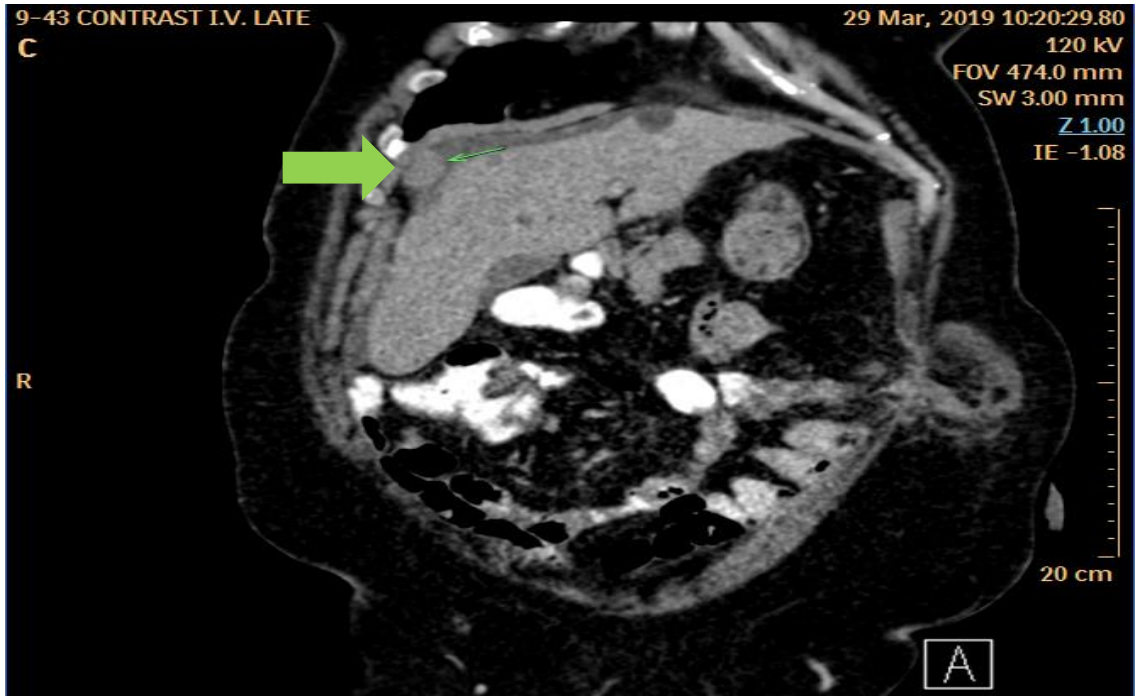
ORIGINAL RESULTS

67,F
- Operated for colon cancer 2017
- Postoperative CEA levels within normal range.

Follow up:
- From 04/2018 – slowly increasing **CEA levels up to 7,72ng/ml**.
- Serial contrast enhanced CT scans and two PET CT scans, performed from 04/2018 to 01/2019 did not show recurrence.

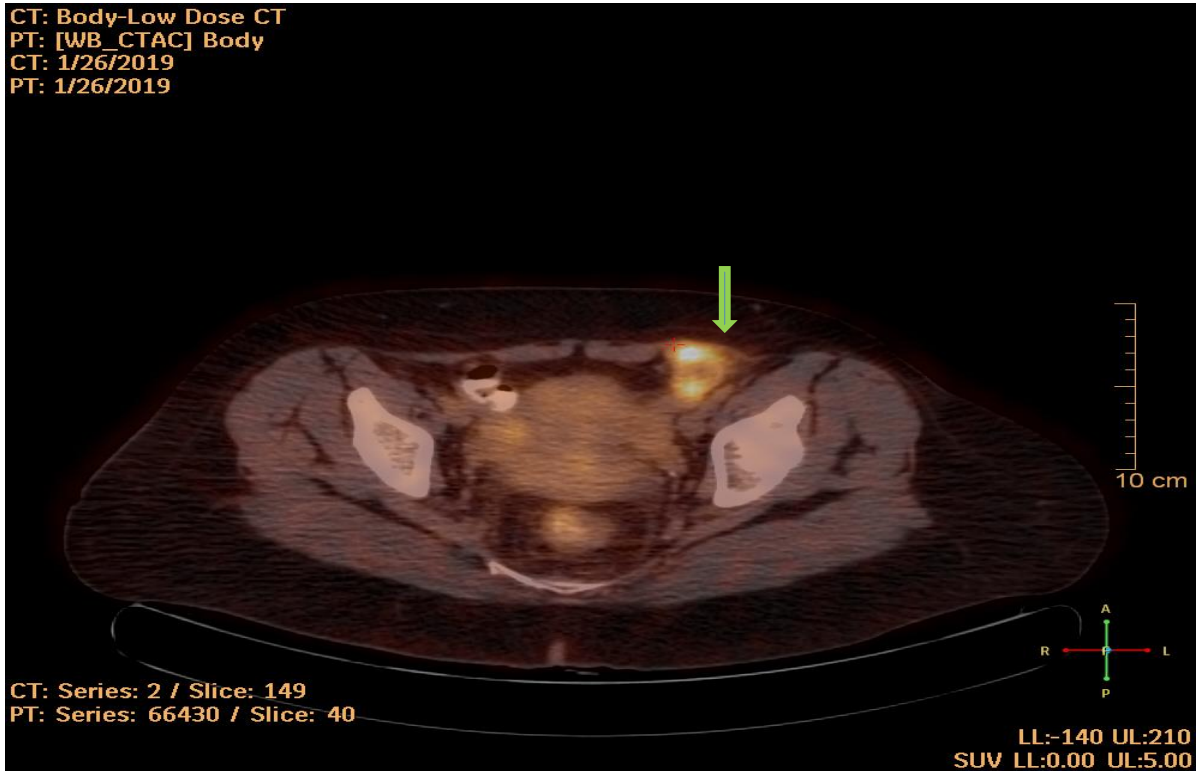
Same patient , three months after last negative CT and PET/CT
- **CEA levels 17,0ng/ml.**
- Contrast enhanced CT scan shows obvious peritoneal metastases and ascites

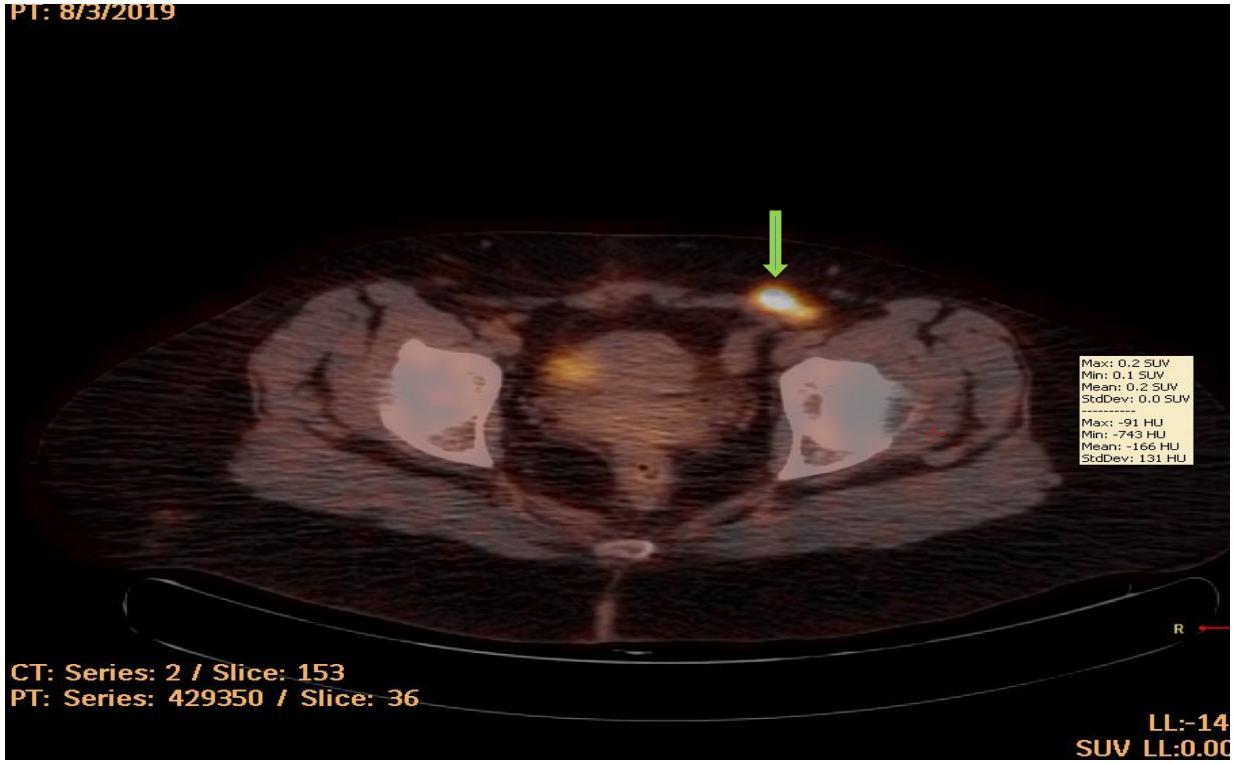




CEA in COLORECTAL MANAGEMENT

ORIGINAL RESULTS





57, F.

- Operated for colon cancer (descendent colon, left hemicolectomy)
- Rising **CEA up to 17ng/ml** on follow up.
- PET/CT scan shows metabolically active lesion close to left ovary and left inguinal channel.
- Surgery: metastasis in soft tissue and left Fallopian tube – complete resection

Same patient

- Postoperative **CEA 5,02 ng/ml**
- PET/CT scan shows metabolically active lesion at the site of operation, almost identical with the preoperative scan.
- Low CEA levels and recent surgery gave confidence on postoperative granuloma being the most probable explanation.
- **Follow up: No recurrence**

CEA in COLORECTAL MANAGEMENT

- The development of new imaging methods and tests for detecting recurrence in patients with colorectal cancer puts on discussion whether and how underestimated is in fact the positive predictive value of CEA, including the levels below 5 ng/ml and whether in patients with higher levels of the marker the oncologist should make a great effort for clearing the reason, i.e. accepting or rejecting a recurrence, or the patient should be followed up using only conventional methods till appearance and verification of clinical symptoms of recurrence.

CONCLUSION

TAKE HOME MESSAGES:

- Although not perfect in predicting recurrence CEA is still the monitoring tool of choice when it comes to colorectal cancer patients.
- Patients with rising CEA levels should be chased to prove recurrence by conventional imaging, endoscopy and FDG PET CT.
- Those with no proof of recurrence should be followed up strictly to define any upward trend of CEA values and in case of such should be reassessed again.

Thanks for your attention!