POSITIVE PREDICTIVE VALUE OF CEA AND Ca19-9 AS TUMOR MARKERS FOR RECURRENT COLORECTAL CANCER IN CASES WHERE CONVENTIONAL WORK-UP FAIL TO LOCALIZE DISEASE

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ABSTRACT

Introduction: Routine surveillance of colorectal cancer includes serial measurements of CEA levels. Although not routinely indicated Ca 19-9 is also a tool for recurrence. When any of these serum markers is elevated during follow up, this could represent a recurrence. The management of elevated tumor marker levels include clinical exams, endoscopy and conventional imaging—ultrasound, CT, MRI.

Objective: To evaluate the positive predictive value of CEA and Ca19-9 as tumor markers for recurrent colorectal cancer in cases where conventional imaging and endoscopic studies fail to localize disease.

Materials and methods: A total of 75 patients with elevated CEA and/or Ca19-9 serum levels and negative endoscopic exam as well as negative abdominal CT and Chest X-ray were included in the study. CEA levels were tested in 50 patients. Ca 19-9 was tested in 65 patients. 34 of the patients had both markers tested. All patients underwent whole body 18F-FDG PET/CT. Patients with negative or equivocal PET scan were further followed up (10 to 24 months).

Results: Based on the reference standard – the results from PET/CT, if positive and the results from follow-up in cases of negative or equivocal scans, the positive predictive value of Ca 19-9 was 84% and that of CEA -83%. There was no significant difference in the PPV of Ca19-9 and CEA.

Conclusion: Elevated CEA and Ca 19-9 levels in patients under active surveillance after operation for colorectal cancer have high positive predictive value for recurrence, even in cases where conventional work-up – endoscopy and CT don't localize disease.

UDC CODE & KEYWORDS

■ UDC: 616.3 ■ Colorectal cancer ■ CEA ■ Ca 19-9 ■ FDG PET/CT

INTRODUCTION

Colorectal cancer is one of the most frequently diagnosed cancers worldwide. It is the third most common cancer in males and the second most common cancer in females as derived from cancer registry databases by Jemal et al (2011). Colorectal is one of the leading causes of cancer-related deaths. Despite these gloomy statistics, the majority of the patients are treated with curative intent. Unfortunately, it tends to recur after initial treatment in nearly one third of the patients as found in a large series of reports by Obrand & Gordon (1997). Given these patients as target population, some large meta-analyses of randomized trials, like those of Rennehan et al (2002) and Figueredo et al (2003), show considerable survival benefits in patients with colorectal cancers on intense follow-up compared to low-intensity follow-up programs. Although some of the trials included especially in the Figueredo et al review failed to prove beneficial. The current opinion of National Comprehensive Cancer Network (NCCN, v.2015) on routine surveillance is that it should include serial measurements of CEA (carcinoembryonic antigen) as well as physical exam every 3-6 months the first 2 years as well as colonoscopy at year 1 and chest, abdominal and pelvic CT annually for the first 2 years. CEA is a glycoprotein, half of which is carbohydrate by structure, with a molecular mass at about 180 kDa. It is a normal content of the colorectal mucosa, vaginal epithelium, some glandular tissues. The highest CEA tissue concentrations are found in primary colorectal carcinomas and their liver metastases. CEA is also expressed in gastric carcinomas, breast and lung cancers. CEA is the first line tumor marker in detection of tumor recurrence in the postoperative monitoring of colorectal carcinomas and in differential diagnosis of liver tumors. For the diagnosis of tumor progression, the positive predictive value of an increase in CEA is between 65 and 84%, the negative predictive value is between 85-90% (Thomas L, Clinical laboratory diagnostics, 1998).

The use of CEA as a screening tumor marker for initial diagnosis of colorectal cancer is controversial and is generally accepted to have low sensitivity and specificity. Fortunately it's not the case in surveillance of patients with colorectal cancer, treated with curative intent. CEA levels should drop to normal in a 4-8 week period after curative resection. Numerous studies have described the role of elevated CEA levels as a predictor of recurrence with sensitivity ranging from 19% to 88% as extrapolated in a comprehensive review from Abyr et al (2006). According to a study from Grassman et al (2007) CEA measurements could be of value even in cases with preoperatively normal CEA levels. The validation of CEA sensitivity and specificity however differ from studies and is based on follow up, conventional imaging and most recently on the additional use of FDG PET/CT. (18F-fluorodesoxyglucose positron-emission tomography/computed tomography). In case of elevated CEA an attempt to localize disease should be made, which includes conventional imaging (CT of chest, abdomen, pelvis) and endoscopic exams, since CEA level directed treatment is not an acceptable strategy. A special issue arises in case conventional work-up fail to localize disease. In these cases further work-up is needed, rather than "wait and see" strategy in an attempt to diagnose more patients in potentially curable stage. The predictive value of elevated CEA levels in these cases is of importance for a decision making in the dilemma of observation vs. further work-up.

The other frequently utilized serum tumor marker for recurrent digestive tract cancers, including colorectal is Ca 19-9. The first report on a monoclonal antibody, which reacted with a human colorectal cancer line, was in 1979 by Koprovski et al.

The antigen isolated had a molecular weight of 36 kD and was named Ca 19-9 or GICA. Biochemically it is a glycolipid, the sialyl derivative of lacto- N- fucopentaose II, a hapten of human Lewis -A-blood group determinant as seen from further works by Magnani et al (1982). It has been detected mainly in cancer of the colon, the stomach, the pancreas, liver, biliary tract, lung, breast, mucinous ovarian cancer. Being a normal component of a Lewis A, in secretions/ such as milk, sputum, saliva, seminal fluid, amniotic fluid, etc. / a physiologically high concentration of Ca 19-9 can be found. CA19-9 is not tumor-specific or organ specific antigen. Suspected presence of pancreatic, hepatobiliary or gastric cancer is defined as an absolute indication for measuring, whether diagnosis and monitoring of colorectal cancer and ovarian cancer is a relative indication. In patients with colorectal cancer it is a second line tumor marker after CEA. The clinical sensitivity of Ca 19-9 for colorectal cancer was initially reported by Del Villano (1983) to be 8-46%, depending on the tumor stage. The clinical specificity of the marker reaches 92-99 % for healthy people and patient with benign disease. It is an independent predictor for survival as a perioperative value with decision level 37 IU/ml, besides the tumor stage according to a study of Diez et al (1994) in multivariate analysis. Although CEA is the elected serum tumor marker for colorectal cancer surveillance, Ca19-9 has also proven to be of value in these patients, although its routine use is discouraged by the European Group on Tumor Markers (EGTM, 2007). However, there is data that Ca 19-9 increase during follow up is as indicative for recurrence as CEA like in the study of Kawamura et al (2010), although controversial data also exist (Nicolini et al, 2010). The reported positive predictive value of Ca 19-9 for recurrence in a study from Park et al (2009) reaches 59% with peritoneal metastases being most frequently associated with elevated marker. Our experience with local practices shows that Ca19-9 in Bulgaria is equally utilized as surveillance marker as CEA. Although Ca 19-9 could rise nonspecifically and due to benign conditions even in healthy subjects (Kim B.J& Lee K.T&Moon T.G, 2009) it poses the same decision making issue as asymptotically elevated CEA, i.e. whether it's increase should result in extensive work-up or not.

Aim of the study was to evaluate the positive predictive value of CEA and Ca19-9 as tumor markers for recurrent colorectal cancer in cases where conventional imaging (CT) and endoscopic studies fail to localize disease.

Materials and methods

75 patients with colorectal cancer, present with elevated CEA and/or Ca 19-9 during follow up after treatment with curative intent (surgery alone or in combination with chemotherapy and/or radiotherapy) in whom conventional work-up failed to localize disease were included in the study. Of all 75 patients 32 were operated for rectal cancer, 22 for tumors of the sigmoid colon, 11 for tumors of ascendant colon, 4 patients with tumors of descendent and 4 of transverse colon and 2 patients with cancer of the coecum. 74 patients were histologically diagnosed with adenocarcinoma and one with mucinous carcinoma.

Conventional workup included the results of the surveillance endoscopy and contrast enhanced abdominal/pelvic CT and chest X-ray as a minimum. In patients with rectal amputation and anus praeter, endoscopic exam was not routinely asked for. MRI and bone scan were not considered part of routine workup, but whenever performed and positive their results worked as exclusion criteria. Patients with known and treated M1 disease were not included in the study, despite negative CT results. The reference diagnosis was obtained by 18F-FDG whole body PET/CT. PET/CT was performed on Phillips Gemini 16TF PET/CT scanner after intravenous administration of 0.13 mCi/kg 18F-FDG with a 60 min uptake period. All patients kept fasting for at least 6 hours before the scan and refrained from tobacco and alkaloid drinks for the same period of time. Blood glucose levels were checked prior to injection. PET/CT was scheduled at least a month after surgery or chemotherapy and at least three months after radiotherapy. The scan itself included Low dose CT (120 keV, up to 100 mAs) from vertex to mid -thigh and a PET acquisition with the same scan field. The scan's FDG PET/CT negative cases (N=11) were further followed up clinically and by imaging. FDG PET/CT positive cases that present with a single site of disease (N=16) or with equivocal findings (N=4) were further verified by surgery (N=8) or follow up (N=12). Cases with multiple metastatic sites on FDG PET/CT imaging were not further studied.

Serum levels of Ca 19-9 were measured in 65 patients and CEA – in 50 patients (in 34 patients both of the markers were measured). We used direct chemiluminescent method for the determination of Ca 19-9. The linearity of the assay was up to 700 IU/ml with a minimum detectable concentration (analytical sensitivity) of 1.2 IU/ml. Reference values for the upper normal limit of Ca19-9 were 37 IU/ml. Every value above that was considered pathologic. For the determination of the serum levels of CEA again direct chemiluminescent method was used. The linearity of the assay was up to 100 ng/ml with a minimum detectable concentration of 0.5 ng/ml. Reference values for the upper normal limit of CEA were 3.4 ng/ml. Every value above what was established as upper limit by the lab which performed the test was considered pathologic.

Results

Ca 19-9 was elevated above reference range upper limit in 55 out of 65 patients in whom the serum levels of the marker were measured (172,1±251,4 U/ml, ranging from 40 U/ml to 1679 U/ml). CEA levels were elevated above reference range upper limit in 46 out of 50 patients, in whom the serum levels were measured (29±56,6 ng/ml, ranging from 3.5 ng/ml to 300 ng/ml). In 40 patients both serum marker levels were measured: CEA levels were elevated in 10 patients with normal Ca 19-9. Ca 19-9 was elevated in 4 patients with normal CEA levels. In the rest 26 patients there was a concordant elevation of both markers.

Since conventional workup, including CT of abdomen and pelvis, chest X-ray and endoscopy were read as negative or inconclusive; all patients underwent whole body FDG PET/CT with the described protocol. 62 of the scans were read as FDG PET positive i.e. diagnostic for malignancy, 4 were read as equivocal and 11 were read as negative. All the patients with negative scans were followed up from 10 months to 2 years with 9 of them showing no evidence of disease. In two patients with negative PET/CT we registered short term progression with lung metastases in one and peritoneal metastases in the other (confirmed by CT on follow up). It's of notice that the patient with highest Ca19-9 serum levels (379 U/ml) in the FDG-negative group had his serum Ca19-9 levels turn close to normal on sequential follow up. There were 4 patients with equivocal/inconclusive FDG PET/CT who were further followed up for verification. The FDG positive cases show various extents of disease and metastatic sites with lymph node involvement being the most common pathology detected. Lymph node metastases were revealed in 24 patients and in 12 of them were the only pathologic finding. This result is

generally expected since CT and MRI as structural imaging modalities assess lymph node involvement by size criteria only, while PET/CT represents metabolic activity. The mean values of Ca 19-9 and CEA in patients with lymph node metastases only were $117,7 \pm 66,1$ U/ml and $44,9 \pm 73,4$ ng/ml respectively. In one patient Ca 19-9 was in normal range opposed to high CEA level. The second most affected site was liver with 19 patients having liver metastases and 9 of them having liver metastases only. Ca 19-9 and CEA levels in cases of isolated liver metastases were $221 \pm 337,8$ U/ml and $58,4 \pm 118,5$ ng/ml respectively. On two occasions serum levels of Ca 19-9 were within normal range. Local recurrence was detected in 18 patients with 12 of them having only isolated recurrence (9 of these with rectal cancer) (Figure 1) Ca 19-9 and CEA levels in patients with isolated local recurrence were $109,1 \pm 108,6$ U/ml and $28,8 \pm 64,4$ ng/ml respectively. On two occasions serum Ca 19-9 levels were within normal range. In three patients CEA levels were normal. Results of these findings as well as details for other metastatic sites are given in Table 1.

Figure 1: 71 year old female operated for rectal cancer, T3N1M0, Ca 19-9 – 53 U/ml/ FDG PET/CT is indicative of local recurrence. Patient was operated and confirmed by pathology

Source: Authors

Table 1: Mean serum concentration of CEA and Ca 19-9 in patients with isolated recurrence or metastatic site. (Locations with very few entries are excluded)

	Number of patients	Ca 19-9 negative	CEA negative	Ca 19-9 (U/ml)	CEA (ng/ml)
Lymph nodes	12	1	0	$117,7 \pm 66,1$	$44,9 \pm 73,4$
Liver	9	2	0	$221 \pm 337,8$	$58,4 \pm 118,5$
Local recurrence	12	2	3	$109,1 \pm 108,6$	$28,8 \pm 64,4$
Lung	2	0	0		
Peritoneum	3	0	0		
Other	3	0	0		
Multiple locations	21	2	0	$173,3 \pm 194,2$	$19,5 \pm 20,4$

Source: Authors

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No significant difference was observed between any marker levels dependent on metastatic site. Among the FDG positive cases there were two patients in whom PET/CT revealed a second malignancy. One of the patients with elevated Ca 19-9 (47 U/ml) had high activity in the prostate, further confirmed by biopsy and prostatectomy, but no evidence of metastatic spread from its primary-colorectal cancer. His Ca19-9 levels turned to normal after the prostatectomy. The second patient had peritoneal metastases and ovarian tumor. Both CEA and Ca 19-9 were elevated in this case. She was operated further on with a histological conformation of ovarian adenocystic cancer. In the analysis of positive predictive value of CEA and Ca 19-9 we analyze these two cases as false positive, which is true if we consider only colorectal cancer-related event rather than malignancy in general.

Based on the FDG PET/CT results and the additional follow up and conformation studies in FDG negative or equivocal cases we defined 60 positive cases as ones having recurrent disease (either local recurrence or metastatic disease or both) and 15 negative cases as ones free of disease. Patients with elevated serum levels of Ca19-9 and CEA were defined as true positive or false positive according to the reference established. Given this basis as referenced standard we calculated the positive predictive value of both Ca 19-9 and CEA as the number of true positive cases, divided by the sum of true positive and false positive cases. The PPV of both markers together was 80%. The PPV of Ca 19-9 was 84% and that of CEA was 83%. There was no significant difference in the PPV of Ca19-9 and CEA.

CONCLUSION

Both Ca 19-9 and CEA have a very high positive predictive value in patients with colorectal cancer, monitored for recurrence, in whom conventional CT imaging and endoscopy fail to localize disease.

Discussion

A major concern on the diagnostic accuracy of tumor markers in colorectal cancer comes from the reference standard used, being it either pathology or imaging and follow up. Studies that utilize imaging use different techniques, ranging from ultrasound, CT, MRI and more recently FDG PET and PET/CT. That's why earlier publications results on CEA accuracy with conventional imaging as reference standard cannot be directly compared to those that include MRI and FDG PET in the work-up as the one of Tan et al (2009). The same could be addressed to Ca19-9 also. Although CT is more sensitive for detection of recurrent disease than any tumor marker it also has its limitations that result in false negative cases. The superiority of MRI and FDG PET/CT is evident in local recurrence detection (MRI) and in the detection of small lymph nodes, peritoneal deposits and local recurrences (especially for rectal cancer) for FDG PET, apparent from studies like those of Fiocchi et al (2011) and Metser et al (2010). Based on this the question whether conventional work-up is sufficient reference to determine diagnostic performance of tumor markers is an object of discussion. Given our results the overall PPV of elevated CEA and Ca19-9 levels in the surveillance process of colorectal cancer patients is expected to be higher if compared to conventional imaging verification since FDG PET/CT and additional follow up adds more true positive cases to the bin of CEA positive cases, verified by CT or endoscopy. The main issue is whether we should address the elevated serum tumor markers as indicative of recurrence despite negative results from other studies or should follow up on regular basis. The hereby presented study provides a positive answer to that question with CEA and Ca19-9 levels being indicative of cancer recurrence in very high proportion of patients. That's true for both CEA and Ca19-9. Both markers have equal PPV for recurrence and their elevation should be a serious red light for the clinicians. The discussion whether this results in more curable cases and thus in improved survival is out of the scope of our study and needs further research with a different primary design.

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